Adverse Drug Events Observed with the Novel Sodium/Glucose Co-Transporter 2 Inhibitor Ipragliflozin for the Treatment of Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-analysis of Randomized Studies

Dan Liu · Hao Chen · Fang Song · Mohamad Anis Ahmed · Hongyan Wu

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is becoming a major issue worldwide. To effectively control the blood sugar of patients with T2DM, several novel oral hypoglycemic agents (OHAs) are being developed. Sodium/glucose co-transporter 2 (SGLT 2) inhibitors have recently shown beneficial outcomes in patients with T2DM. In this analysis, we aimed to systematically compare the adverse drug events observed with ipragliflozin versus placebo for the treatment of patients with T2DM.

Methods: <http://www.ClinicalTrials.gov>, the bibliographic database of life science and

biomedical information MEDLINE, EMBASE and the Cochrane Central were searched for English publications satisfying the inclusion and exclusion criteria of this study. Adverse drug events were the end points in this analysis. The latest version (5.4) of the RevMan software was used to analyze the data, and risk ratios (RR) with 95% confidence intervals (CI) were used to represent the data post analysis.

Results: Eight randomized studies with a total of 1519 participants with T2DM were included in this analysis whereby total treatment-emergent adverse events (RR: 1.06, 95% CI: 0.96–1.16; $P = 0.26$), including mild (RR: 0.95, 95% CI: 0.79–1.13; $P = 0.54$), moderate (RR: 1.04, 95% CI: 0.72–1.51; $P = 0.83$) and severe treatment-emergent adverse events (RR: 0.72, 95% CI: 0.26–1.96; $P = 0.52$), were not significantly different in those patients who were assigned to ipragliflozin versus placebo for the treatment of T2DM. Moreover, drug-related adverse events (RR: 1.04, 95% CI: 0.69–1.58; $P = 0.85$), adverse events leading to drug discontinuation (RR: 1.09, 95% CI: 0.57–2.10; $P = 0.79$), urinary tract infection (RR: 1.03, 95% CI: 0.60–1.77; $P = 0.91$), naso-pharyngitis (RR: 0.54, 95% CI: 0.19–1.52; $P = 0.25$), constipation (RR: 1.94, 95% CI: 0.90–4.20; $P = 0.09$), dizziness (RR: 0.81, 95% CI: 0.20–3.23; $P = 0.76$), gastrointestinal disorders (RR: 0.96, 95% CI: 0.68–1.36; $P = 0.82$) and dehydration (RR: 2.26, 95% CI: 0.38–13.43; $P = 0.37$) were also not significantly different. However, genital

Drs. Dan Liu and Hao Chen contributed equally to this article and are the first co-authors.

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D. Liu · H. Chen · F. Song · H. Wu (✉)
Department of Endocrinology, The First Affiliated
Hospital of Yangtze University, Jingzhou First
People's Hospital, Jingzhou, Hubei, People's
Republic of China
e-mail: wcls2020720@163.com

M. A. Ahmed
Department of Cardiology, Peking University
People's Hospital, Beijing, People's Republic of
China

infection (RR: 4.53, 95% CI: 1.48–13.85; $P = 0.008$) and hypoglycemia (RR: 1.68, 95% CI: 1.03–2.74; $P = 0.04$) rates were significantly higher in the ipragliflozin group.

Conclusions: The current analysis showed ipragliflozin to be associated with significantly higher genital infection rates compared to placebo, whereas no significant difference was observed compared to the other adverse drug events in these patients with T2DM. In addition, hypoglycemia was also not significantly different following sensitivity analysis.

Keywords: Adverse drug events; Genital infection; Hypoglycemia; Ipragliflozin; Type 2 diabetes mellitus

Key Summary Points

Why carry out this study?

Type 2 diabetes mellitus (T2DM) is becoming a major issue worldwide. To effectively control the blood sugar of patients with T2DM, several novel oral hypoglycemic agents (OHAs) are being developed.

Sodium/glucose co-transporter 2 (SGLT 2) inhibitors have recently shown beneficial outcomes in patients with T2DM.

What was learned from the study?

In this analysis, we aimed to systematically compare the adverse drug events observed with ipragliflozin versus placebo for the treatment of patients with T2DM.

Ipragliflozin was associated with significantly higher genital infection rates compared to placebo, whereas no significant difference was observed compared to the other adverse drug events in these patients with T2DM.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is becoming a major issue worldwide [1]. To effectively control the blood sugar of patients with T2DM, several novel oral hypoglycemic agents (OHAs) are being developed [2]. Sodium/glucose co-transporter 2 (SGLT 2) inhibitors have recently shown beneficial outcomes in the treatment of patients with T2DM [3].

Ipragliflozin, a novel SGLT 2 inhibitor that was jointly developed by Astellas Pharma and Kotobuki Pharmaceuticals, was approved for the treatment of patients with T2DM in January 2014 [4]. Since then, several studies based on Japanese participants have shown beneficial effects of ipragliflozin compared to placebo [5].

The Fukuoka Study of Ipragliflozin (FUSION) showed several positive outcomes related to glycemic control and cardiovascular parameters in Japanese patients who were treated for T2DM [6]. The interim outcome of the ASSIGN-K Study, which was based on Japanese T2DM participants, also showed ipragliflozin to improve glycemic control and weight loss [7]. Nevertheless, even if adverse drug events were also reported in certain studies, they were never systematically assessed.

In this analysis, we aimed to systematically compare the adverse drug events observed with ipragliflozin versus placebo for the treatment of patients with T2DM.

METHODS

Search Databases

<http://www.ClinicalTrials.gov>, the bibliographic database of life science and biomedical information MEDLINE, EMBASE and the Cochrane Central were the electronic databases searched for English publications satisfying the inclusion and exclusion criteria listed below.

Search Terms

The following search terms were considered:

- Ipragliflozin and type 2 diabetes mellitus;
- Ipragliflozin and diabetes mellitus;
- Ipragliflozin and adverse drug outcomes;
- Ipragliflozin and T2DM;
- Novel sodium-glucose co-transporter 2 inhibitor and diabetes mellitus.

These terms were searched from the above-mentioned online databases with adherence to the PRISMA study guideline [8].

Inclusion Criteria

Studies were included if:

- (a) They were randomized trials comparing ipragliflozin versus placebo for the treatment of patients with T2DM;
- (b) They reported adverse drug events as their clinical end points;
- (c) They reported any follow-up time period.

Exclusion Criteria

Studies were excluded if:

- (a) They were observational studies/meta-analyses/review of literature/case studies/letters to editors;
- (b) They did not compare ipragliflozin versus placebo;
- (c) They did not report adverse drug events as their clinical end points;
- (d) They were duplicated/repeated studies.

Participants, Outcomes and Follow-up

All the participants included in this analysis were patients with T2DM who were treated with ipragliflozin or placebo.

The following end points were assessed in this analysis (Table 1):

- (a) Total treatment-emergent adverse events (TEAEs);
- (b) Mild TEAEs;
- (c) Moderate TEAEs;
- (d) Severe TEAEs;

- (e) Drug-related adverse events;
- (f) Adverse events leading to drug discontinuation;
- (g) Hypoglycemia;
- (h) Urinary tract infection;
- (i) Genital infection;
- (j) Naso-pharyngitis;
- (k) Constipation;
- (l) Dizziness;
- (m) Gastrointestinal disorders;
- (n) Dehydration.

The follow-up time period varied from 2 to 52 weeks as reported in the original studies.

Data Extraction and Quality Assessment

Important data including the total number of participants assigned to the ipragliflozin and placebo groups, respectively, reported outcomes, follow-up time periods, total number of events representing each end point, baseline features and other main features that were required in this analysis were carefully extracted by the reviewers. Any disagreement that followed was resolved by consensus.

The methodologic quality of the randomized trials was assessed with significant attention given to the criteria recommended by the Cochrane Collaboration [9]. Bias was reported as being of low, moderate or high risk.

Statistical Analysis

The latest version (5.4) of RevMan software was used to analyze the data. Risk ratios (RRs) and 95% confidence intervals (CIs) were used to represent the data post analysis.

Heterogeneity was assessed by the Q statistic test. An analysis involving a P value ≤ 0.05 was considered statistically significant, whereas any P value > 0.05 was considered statistically insignificant.

Heterogeneity was also assessed by the I^2 statistic test. The higher the value of I^2 , the higher the heterogeneity was.

The statistical models used included a fixed effect (if $I^2 < 50\%$) and a random effect

Table 1 End points and follow-up time periods

Randomized studies	Adverse drug events reported	Follow-up time period	Type of participants
Fonseca 2012 [10]	TEAEs (mild, moderate, severe), drug-related AEs, drug-related AEs leading to permanent discontinuation of therapy, hypoglycemia, UTI, GI disorders	12 weeks	Type 2 DM
Han 2018 [11]	TEAEs (mild, moderate, severe), drug-related AEs, drug-related AEs leading to permanent discontinuation of therapy, naso-pharyngitis, urticarial, gastritis, ALT increased, AST increased, hypoglycemia, UTI, genital infection, dehydration	24 weeks	Type 2 DM
Ishihara 2016 [12]	TEAEs, drug-related AEs, drug-related AEs leading to permanent discontinuation of therapy, hypoglycemia, UTI, increased blood ketone bodies, vulvo-vaginal candidiasis, muscle spasm, constipation, rash, cerebral infarction, dizziness, dehydration	16 weeks	Type 2 DM
Kashiwagi 2015 [13]	TEAEs, drug-related AEs, drug-related AEs leading to permanent discontinuation of therapy, hypoglycemia, UTI, genital infection	52 weeks	Type 2 DM
Lu 2016 [14]	TEAEs (mild, moderate, severe), drug-related AEs, drug-related AEs leading to permanent discontinuation of therapy, naso-pharyngitis, osteoarthritis, UTI, dizziness, dysuria, constipation	24 weeks	Type 2 DM
Schwartz 2011 [15]	TEAEs, GI disorders, constipation, nausea, nervous system disorders	2 weeks	Type 2 DM
Veltkamp 2012 [16]	TEAEs (mild, moderate, severe), drug-related AEs, drug-related, naso-pharyngitis, GI disorders, nausea, dehydration	2 weeks	Type 2 DM
Wilding 2012 [17]	TEAEs (mild, moderate, severe), drug-related AEs, drug-related AEs leading to permanent discontinuation of therapy, hypoglycemia, UTI, GI disorders, urticarial, rash, nervous system disorder, UTI, genital infection	12 weeks	Type 2 DM

DM diabetes mellitus, TEAEs treatment-emergent adverse events, AEs adverse events, UTI urinary tract infection, GI gastrointestinal

($I^2 > 50\%$) model depending on the I^2 value obtained.

Sensitivity analysis was carried out by an exclusion method.

Publication bias was visually assessed through funnel plots for this analysis with a low study volume.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with

human participants or animals performed by any of the authors.

RESULTS

Search Outcomes

A total of 1475 publications were obtained from the search databases. After elimination of irrelevant articles, 78 full-text publications were assessed for eligibility.

Further full-text articles were eliminated based on the following criteria:

- Meta-analyses/literature reviews/observational studies/case studies/letters to editors (7);
- Reported only efficacy outcomes without mentioning adverse drug events (4);
- Did not involve a placebo group (5);
- Reported data that could not be used in this analysis (3);
- Protocol of previous or upcoming trials (5);
- Duplicated studies (46).

Finally, only eight randomized studies [10–17] were confirmed for this analysis, as shown in Fig. 1.

Features of the Randomized Studies and the Included Participants

Eight randomized studies with a total of 1519 participants with T2DM (1069 were assigned to

ipragliflozin and 450 to placebo) were included in this analysis. The time period of patient enrollment varied from the years 2011 to 2017, as shown in Table 2.

Table 3 lists the baseline features of the participants. The participants had mean age ranging from 53.3 to 65.7 years with a predominance of male participants. HbA1c varied from 7.53 to 8.67%. Duration of diabetes mellitus varied from 4.67 to 14.3 years.

Main Results of This Analysis

This analysis showed that total treatment-emergent adverse events (RR: 1.06, 95% CI: 0.96–1.16; $P = 0.26$), including mild treatment-emergent adverse events (RR: 0.95, 95% CI: 0.79–1.13; $P = 0.54$), moderate treatment-emergent adverse events (RR: 1.04, 95% CI: 0.72–1.51; $P = 0.83$) and severe treatment-

Fig. 1 Flow diagram representing the study selection (PRISMA guideline)

Table 2 Main features of the randomized studies

Studies	Type of study	Total no. of participants assigned to ipragliflozin (<i>n</i>)	Total no. of participants assigned to placebo (<i>n</i>)	Time period of patients' enrollment
Fonseca 2012	RT	273	69	–
Han 2018	RT	74	68	2015–2017
Ishihara 2016	RT	175	87	2014–2015
Kashiwagi 2015	RT	118	46	2011–2012
Lu 2016	RT	87	83	2011–2013
Schwartz 2011	RT	48	13	–
Veltkamp 2012	RT	18	18	2009
Wilding 2012	RT	276	66	–
Total no. of participants (<i>n</i>)		1069	450	

RT randomized trials

Table 3 Baseline features of the patients with type 2 diabetes mellitus

Studies	Age (years) Ipra/placebo	Males (%) Ipra/placebo	HbA1c (%) Ipra/placebo	Duration of DM (years) Ipra/placebo	BMI (kg/m ²) Ipra/placebo
Fonseca 2012	53.7/53.4	50.9/46.4	7.93/7.84	4.57/4.64	31.2/30.9
Han 2018	57.6/57.4	50.7/48.5	7.90/7.92	11.6/11.3	25.5/26.05
Ishihara 2016	58.7/59.2	62.5/58.6	8.67/8.62	12.6/14.3	25.6/26.4
Kashiwagi 2015	63.9/65.7	78.0/78.3	7.53/7.55	9.50/9.40	25.8/24.9
Schwartz 2011	57.9/53.3	54.2/69.2	–	–	32.5/32.4
Veltkamp 2012	58.9/55.8	66.7/72.2	–	–	31.1/31.1
Wilding 2012	57.5/57.3	50.4/54.5	7.79/7.68	6.00/5.70	31.7/32.0

HbA1c glycated hemoglobin, *DM* diabetes mellitus, *BMI* body mass index, *kg* kilogram, *m*² square meter, *Ipra* ipragliflozin group

emergent adverse events (RR: 0.72, 95% CI: 0.26–1.96; *P* = 0.52) were not significantly different in those patients who were assigned to ipragliflozin versus placebo for the treatment of T2DM, as shown in Fig. 2.

Moreover, drug-related adverse events (RR: 1.04, 95% CI: 0.69–1.58; *P* = 0.85), adverse events leading to drug discontinuation (RR: 1.09, 95% CI: 0.57–2.10; *P* = 0.79), urinary tract

infection (RR: 1.03, 95% CI: 0.60–1.77; *P* = 0.91), naso-pharyngitis (RR: 0.54, 95% CI: 0.19–1.52; *P* = 0.25), constipation (RR: 1.94, 95% CI: 0.90–4.20; *P* = 0.09), dizziness (RR: 0.81, 95% CI: 0.20–3.23; *P* = 0.76), gastrointestinal disorders (RR: 0.96, 95% CI: 0.68–1.36; *P* = 0.82) and dehydration (RR: 2.26, 95% CI: 0.38–13.43; *P* = 0.37) were also not significantly different, as shown in Figs. 3 and 4.

Fig. 2 Adverse drug events observed with ipragliflozin versus placebo for the treatment of patients with type 2 diabetes mellitus

However, genital infection (RR: 4.53, 95% CI: 1.48–13.85; $P = 0.008$) and hypoglycemia (RR: 1.68, 95% CI: 1.03–2.74; $P = 0.04$) rates

were significantly higher in patients who were assigned to ipragliflozin, as shown in Fig. 3.

The results were summarized in Table 4.

◀ **Fig. 3** Individual adverse drug events observed with ipragliflozin versus placebo for the treatment of patients with type 2 diabetes mellitus

Sensitivity Analysis and Publication Bias

When sensitivity analysis was carried out, excluding the Fonseca (2012) study (RR: 1.69, 95% CI: 1.03–2.78; $P = 0.04$), excluding the Han (2018) study (RR: 1.77, 95% CI: 1.07–2.93; $P = 0.03$), excluding the Kashiwagi (2015) study (RR: 1.69, 95% CI: 1.03–2.78; $P = 0.04$) and excluding the Wilding (2012) study (RR: 1.77, 95% CI: 1.05–2.98; $P = 0.03$) did not show any significant difference compared to the main result, which already showed hypoglycemia to be significantly higher with ipragliflozin. However, excluding the Ishihara (2016) study (RR: 0.92, 95% CI: 0.30–2.85; $P = 0.89$) showed hypoglycemia was not significantly higher with ipragliflozin. Sensitivity analysis showed that the main result representing hypoglycemia was influenced by the Ishihara (2016) study and that hypoglycemia might actually not have been significantly higher in those patients who were treated with ipragliflozin. For all the other subgroups, sensitivity analyses showed consistent results throughout.

Publication bias was visually assessed through funnel plots, and low evidence of publication bias was observed across all the randomized studies that assessed the different adverse drug events throughout, as shown in Figs. 5 and 6.

DISCUSSION

Ipragliflozin, a novel SGLT2 inhibitor, was approved in Japan for the treatment of patients with T2DM in January 2014. Several Japan-based studies have shown this drug to have to be well tolerated by the participants.

In this analysis, where the adverse drug events were compared with ipragliflozin versus placebo, it was found that no significant difference was noted in treatment-emergent adverse events (mild, moderate or severe) and that ipragliflozin was associated with similar rates of urinary tract infection, gastrointestinal disorders, dehydration and other events described in the Results section. However, the genital infection rate was significantly higher with ipragliflozin.

Even though our result showed hypoglycemia to be significantly higher with ipragliflozin, sensitivity analyses showed that this result was highly influenced by the data from

Fig. 4 Drug-related adverse events observed with ipragliflozin versus placebo for the treatment of patients with type 2 diabetes mellitus

Table 4 Summarized results

Adverse drug events assessed	RR with 95% CI	<i>P</i> value	<i>I</i> ² (%)
Total TEAEs	1.06 [0.96–1.16]	0.26	37
Mild TEAEs	0.95 [0.79–1.13]	0.54	0
Moderate TEAEs	1.04 [0.72–1.51]	0.83	0
Severe TEAEs	0.72 [0.26–1.96]	0.52	0
Drug-related adverse events	1.04 [0.69–1.58]	0.85	65
AEs leading to drug discontinuation	1.09 [0.57–2.10]	0.79	0
Hypoglycemia	1.68 [1.03–2.74]	0.04	0
Urinary tract infection	1.03 [0.60–1.77]	0.91	0
Genital infection	4.53 [1.48–13.85]	0.008	0
Naso-pharyngitis	0.54 [0.19–1.52]	0.25	0
Constipation	1.94 [0.90–4.20]	0.09	0
Dizziness	0.81 [0.20–3.23]	0.76	26
Gastrointestinal disorders	0.96 [0.68–1.36]	0.82	11
Dehydration	2.26 [0.38–13.43]	0.37	0

RR risk ratios, CI confidence intervals, TEAEs treatment-emergent adverse events, AEs adverse events

Fig. 5 Funnel plot representing publication bias (A)

Fig. 6 Funnel plot representing publication bias (B)

one particular study. Excluding that particular study showed a similar hypoglycemia risk with ipragliflozin versus placebo throughout.

A recently published meta-analysis showed class one evidence that ipragliflozin is effective and safe to use as mono- or add-on therapy to other oral hypoglycemic agents for the treatment of patients with T2DM [18]. It should be noted that the analysis compared the efficacy and safety outcomes, whereas our analysis compared the adverse drug events. Our results showed significantly higher genital infection rates to be associated with the use of ipragliflozin, which makes this the usefulness of this treatment doubtful.

The STELLA-ELDER trial also showed that this drug was well tolerated in patients with T2DM even though a small percentage of the participants had genital infections [19]. Hypoglycemia and genital infections were of a non-

serious type. Even during the long term, as shown in the interim results of the STELLA-Long-Term post-marketing surveillance study, ipragliflozin was still well tolerated and effective in Japanese patients with T2DM without showing any new safety issues [20].

Additionally, even though diabetic ketoacidosis was not assessed in this current paper, some studies have also reported ketoacidosis following the administration of ipragliflozin [21]. Therefore, it is recommended to monitor euglycemic ketoacidosis following the discontinuation of ipragliflozin especially in those patients who do not feel well after discontinuing the drug. Other important adverse outcomes of ipragliflozin could include dehydration and frailty. A study even mentioned that ipragliflozin should be used cautiously in elderly patients because of a higher risk of renal impairment, orthostatic hypotension and dehydration [22].

Limitations

The following limitations were reported in this analysis: the total number of participants might not have been sufficient to reach a robust conclusion. In addition, several studies also included an add-on of metformin or insulin with ipragliflozin, and this could have influenced the results. In addition, the duration of disease was not similar in all the studies. Another limitation could be the fact that the dosage of ipragliflozin was not taken into consideration. Moreover, result of the subgroup assessing for hypoglycemia was highly influenced by data from the Ishihara (2016) study showing a significant increase in hypoglycemia with ipragliflozin. However, sensitivity analysis showed that hypoglycemia was not significantly different with ipragliflozin compared to placebo. Another limitation could be the fact that the cardiovascular outcomes were not assessed in this analysis. Cardiovascular outcomes were not reported in the original trials, and our study was only based on the adverse drug reactions. Finally, even if systematic reviews and meta-analyses showed a high evidence level, sometimes rare and severe adverse events cannot be detected in randomized trials because of shorter follow-up time periods in those trials, and this could be another potential limitation of this analysis.

CONCLUSIONS

The current analysis showed ipragliflozin to be associated with significantly higher genital infection rates compared with placebo, whereas no significant difference was observed for the other adverse drug events in these patients with T2DM. In addition, hypoglycemia was also not significantly different following sensitivity analysis.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. All data generated or analyzed during this study are included in this published article. References to the original publications have also been provided and are publicly available in all the search databases including MEDLINE, EMBASE and so on.

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