Incretin-based therapies for type 2 diabetes mellitus in Asian patients: Analysis of clinical trials

Melva Louisa,1 Madoka Takeuchi,2 Masahiroy Takeuchi,2 Nafrialdi,1, Rianto Setiabudy1

1 Department of Pharmacology and Therapeutics, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia
2 Department of Biostatistics and Clinical Medicine, Kitasato University

Abstrak

Tujuan untuk meninjau efisiensi dan keamanan terapi diabetes melitus tipe 2 berbasis inkretin (incretin-based therapy) yang saat ini beredar (eksenatid, liraglutid, sitagliptin, vildagliptin) pada populasi Asia.

Metode Kami melakukan pencarian data uji klinik acak yang relevan pada MEDLINE mengenai terapi berbasis inkretin pada diabetes melitus tipe 2 populasi Asia. Data yang digunakan adalah data efisiensi dan keamanan GLP-1 (glucagon-like peptide-1) mimetik dan penghambat DPP-4 (dypeptidyl peptidase-4)

Hasil Empat belas uji klinik acak terapi berbasis inkretin yang mengikutsertakan 3567 pasien diabetes melitus tipe 2 pada populasi Asia (Jepang, Cina, Korea, India). Terapi berbasis inkretin memperbaiki HbA1c lebih besar (hingga -1,42% pada exenatide 10 mcg bid, -1,85% pada liraglutide 0,9 mg qd, -1,4% pada sitagliptin 100 mg dan -1,4% pada vildagliptin 50 mg bid) dibandingkan dengan yang ditemukan pada uji klinik populasi Kaukasia, dengan profil keamanan yang setara.


Abstract

Aim To review the efficacy and safety data on incretin-based therapies currently available (exenatide, liraglutide, sitagliptin, vildagliptin) for the treatment of type 2 diabetes mellitus in Asian population.

Methods We conducted Medline search of all relevant randomized clinical trials of incretin-based therapies for type 2 diabetes mellitus in Asian populations. Data pertinent to the efficacy and safety of GLP-1 mimetics and DPP-4 inhibitors were extracted and used.

Results We found 14 randomized controlled trials of incretin-based-therapy which included 3567 type 2 diabetes mellitus in Asian population (Japanese, Chinese, Korean, Indian). It was shown that incretin-based therapies improved HbA1c at higher extent (up to -1.42% in exenatide 10 mcg bid, -1.85% for liraglutide 0.9 mg qd, -1.4% for sitagliptin 100 mg and -1.4% for vildagliptin 50 mg bid) compared to the effects observed in studies with Caucasian population, with comparable safety profile.

Conclusion The efficacy of incretin-based therapies in Asian patients improved glycemic parameters in a higher magnitude on some glycemic parameters compared with those in Caucasian population. These results indicate that incretin-based therapies may be more effective in Asian population than in Caucasian. (Med J Indones 2010; 19: 205-12)

Key words: exenatide, incretin, liraglutide, sitagliptin, type-2 diabetes, vildagliptin

Type 2 diabetes mellitus is recognized as a major problem worldwide, with a substantial impacts on morbidity, mortality, quality of life and health care cost.1 The WHO estimates that between 2000 and 2030, the world population will increase by 37% and the number of people with diabetes will increase by 114%.2 In Asia, the proportions of people with type 2 diabetes and obesity are increasing consistently. The Asian region is of prime importance because people in Asia constitute 60% of the world’s population.3 Asian population are racially heterogeneous and have differing demographic, cultural and socioeconomic characteristics. Differences in genetic and environmental attributes affecting diabetogenesis and treatment response to medication could also be heterogenous.1,4

The increase in type 2 diabetes in Asia differs from that reported in other parts of the world: it develops in a much shorter time, in a younger age group and in people in a much lower body-mass index (BMI). The reasons for ethnic differences in the risk of type 2 diabetes are not entirely understood.1

The major etiological components of type 2 diabetes are impaired insulin secretion and impaired insulin action, which are aggravated by the presence and degree of glucotoxicity. Both components might also

Correspondence email to: melva.louisa@yahoo.com
be genetically predetermined. Lipotoxicity plays an important part in causing insulin resistance and beta-cell damage. Lipotoxicity plays an important part in causing insulin resistance and beta-cell damage.

Reports from WHO multinational study and DECODE-DECODA study, showed that both insulin resistance and insulin secretion capacity are higher in Caucasians. Ethnic difference among Asian population has also been investigated. DECODA study showed that Asian Indians had a higher prevalence of diabetes compared with Chinese and Japanese. In this study Chinese and Japanese showed almost the same profile of increase in fasting and postprandial glucose with age. In the follow up to the WHO multinational study of vascular disease in diabetes, it was shown that BMI in Japanese patients was much lower than patients in any of the nations investigated, including Chinese.

In Europe and the USA, insulin resistance with obesity is the predominant pathological manifestation of diabetes; in Asia, impaired insulin secretion is predominant. Influx secretory capacity in Japanese patients with type 2 diabetes has shown to have been half of that seen in Caucasian patients, a difference that is particularly pronounced for meal-related secretion.

The incretin hormones released from the gut upon ingestion of meals stimulate insulin secretion. Evidences suggest that 2 most important incretins are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). Both hormones powerfully enhance insulin secretion. While both Asian and Western type 2 diabetes patients generally exhibit incretin defects, they may be more dramatic in Asian patients. Studies by Nauck et al. indicated that the incretin effect is severely reduced or lost in relatively lean type 2 diabetic patients. It is noteworthy that GIP is markedly reduced in Type 2 diabetes mellitus in Asia, while the effectiveness of GLP-1 is generally preserved.

The progressive understanding of incretin pathophysiology has made this pathway an attractive target for development of new anti-diabetic agents. Two approaches have been pursued to develop incretin-based anti-diabetic agents: injectable GLP-1 mimetics or analogues, consisting in molecules modified from the native GLP-1 in order to evade DPP-4 inactivation (endogenous GLP-1 itself has a very short half life due to inactivation of enzyme dipeptidyl peptidase-4/DPP-4); and inhibitors of DPP-4, which aim to enhance endogenous GLP-1 and GIP.

To date there are two GLP-1 mimetics (exenatide and liraglutide) and two DPP-4 inhibitors (sitagliptin and vildagliptin) have been approved by regulatory authority across Asian countries. This review will focus on assessing the efficacy and safety of incretin-based therapy for the treatment of type 2 diabetes in Asian population based on randomized controlled trials published in peer-reviewed journals.

METHODS

Data Sources

We conducted a Medline search from inception to November 2009, for randomized controlled trials of incretin-based therapies for type 2 diabetes mellitus in Asian population that were published in English-language peer-reviewed journals. Other relevant literature sources such as clinical trials databases were also searched (www.clinicaltrials.gov, www.clinicalstudyresults.org, www.controlled-trials.com).

Study selection

Data pertinent to the efficacy and safety of GLP-1 mimetics and DPP-4 inhibitors were extracted and used. Studies were included if they met the following criteria: (1) randomized controlled trials with type 2 diabetes, (2) conducted in Asian country settings with Asian ethnic groups, (3) evaluated effect of the drug on HbA1c, (4) published in English language in a peer-reviewed journal.

RESULTS

We found 14 randomized controlled trials of incretin based-therapy which included 3567 type 2 diabetes mellitus in Asian population (Japanese, Chinese, Korean, Indian) (Table 1). The shortest period of therapy was 10 weeks and the longest was 52 weeks (12 weeks placebo-controlled therapy with additional 40 weeks of extension therapy open label, active treatment).

GLP-1 Receptor Agonists/GLP-1 Mimetics

GLP-1 receptor agonists represent a class of therapies that leverage the glucoregulatory effects of the endogenous incretin hormone GLP-1. This class of agents now includes the subcutaneously injected compounds exenatide and liraglutide.
Exenatide was originally derived from the salivary glands of the Gila monster which has 53% homology with human GLP-1 and found more stable and less rapidly degraded than GLP-1. Exenatide is indicated as an adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus in combination with metformin, sulfonylurea or thiazolidinedione. Exenatide doses are 5 or 10 μg by two subcutaneous injections per day.15,16

We found 3 studies of exenatide (Table 1) which included 649 Chinese, Indians, Korean and Japanese type 2 diabetes patients. In these three placebo-controlled clinical trials, exenatide was given as combination therapy with metformin, sulfonylurea, biguanide, thiazolidinedione or combinations of these agents. Compared with placebo, exenatide induced reductions of HbA1c from -0.6 up to -1.42 % (placebo adjusted), fasting plasma glucose up to -1.2 mmol/L and body weight (-1.2 kg) in a dose-dependent manner. Adverse events reported in these three studies were predominantly gastrointestinal (nausea, vomiting, diarrhea), nasopharyngitis and hypoglycemia.17-19

Liraglutide is a human GLP-1 analog with 97% homology with GLP-1 and is longer acting than exenatide because of an attached free fatty acid derivative that increases non-covalent binding to albumin and renders it more resistant to DPP-4 degradation, which slows renal clearance and absorption from the subcutaneous injection site. Its half life is about 12 hours, allowing it to be administered once daily. Like GLP-1 and exenatide, liraglutide needs to be injected subcutaneously.20

To date, there are 3 studies of liraglutide in Asian population. All of the studies were done in Japanese population which included 890 type 2 diabetes patients. The studies were monotherapy and combination therapy. Liraglutide up to 0.9 mg/day improved HbA1c up to -1.36% (placebo-adjusted), fasting plasma glucose (-2.43 mmol/L).21-23 In the monotherapy study, it was reported that liraglutide 0.9 mg/day decreased body weight by -2.3 kg,22 while in the combination study with other OAD, liraglutide was shown to have a neutral effect on body weight.21,22 Homeostasis model assessment for β-cell function (HOMA-β) and insulin resistance (HOMA-IR) are two widely used parameters to assess beta cell function and the degree of insulin resistance. Lower doses of liraglutide (0.1 mg qd and 0.3 mg qd) did not have beneficial effects toward HOMA-IR and HOMA-β, while higher doses (0.6 mg qd and 0.9 mg qd) decreased HOMA-IR (-0.32 and -0.53) and increased HOMA-β (22 and 21.05 μU/mL), respectively.23 Liraglutide was well-tolerated in the three studies. The most common adverse events were gastrointestinal disorders and infections. Liraglutide did not cause hypoglycemia as observed in exenatide studies.

**DPP-4 inhibitors**

DPP-4 inhibitors (sitagliptin and vildagliptin) have been successfully developed for clinical use; the magnitude of their effect on GLP-1 is limited to the available endogenous levels of the hormone, which may render them less effective than GLP-1 receptor agonists.10,15 However, DPP-4 inhibitors can be administered orally while GLP-1 agonists require administration by injection.

DPP-4 activity is reduced by almost 100% within 15 to 30 minutes of oral administration of DPP-4 inhibitors sitagliptin or vildagliptin, producing 2-fold increase in mean active GLP-1 levels, with a duration of inhibition in excess of 15 hours because of initial rapid binding to DPP-4, followed by slow phase of tight binding, so that effects persist for 24 hours after administration of a single dose of sitagliptin and vildagliptin.22

Currently (December 2009) there are 7 published studies of sitagliptin in Chinese patients with diabetes mellitus and chronic renal insufficiency.27 Sitagliptin reduced HbA1c up to -1.05% (placebo adjusted) and fasting plasma glucose up to -1.4 mmol/L. All of the studies showed that sitagliptin has a neutral effect on body weight, except for the Kadowaki study that showed sitagliptin increased body weight by +0.42 kg. The Nonaka study showed that sitagliptin 100 mg qd decreased HOMA-IR (-0.15) and improved HOMA-β by 9.5 μU/mL. Vildagliptin 50 mg bid in Japanese patients reduced HbA1c by 1.2% (placebo adjusted), fasting plasma glucose by 1.4 mmol/L, body weight by 0.4 kg, HOMA-IR by 0.4 and increased HOMA-β by 8.2 μU/mL. The most common adverse events were gastrointestinal effects and infections (nasopharyngitis, pharyngitis, upper respiratory tract inflammation).
Table 1. Summary of randomized controlled clinical trials with exenatide, liraglutide, sitagliptin and vildagliptin in Asian patients

<table>
<thead>
<tr>
<th>Source</th>
<th>Type of therapy</th>
<th>Trial design</th>
<th>Incretin-based therapy</th>
<th>Comparator Therapy</th>
<th>Therapy duration</th>
<th>Population</th>
<th>No of patients randomized</th>
<th>Δ HbA1c (%)</th>
<th>Comparator subtracted Δ HbA1c (%)</th>
<th>Δ FPG (mmol/L)</th>
<th>Δ weight (kg)</th>
<th>HOMAIR</th>
<th>HOMA Beta (μU/mL)</th>
<th>Most common adverse events in incretin-based therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exenatide</strong></td>
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</tr>
<tr>
<td>Gao 2009</td>
<td>Add on to metformin or sulfonylurea</td>
<td>randomized, double blind, placebo-controlled</td>
<td>Exenatide 5 μg bid for 4 weeks then 10 μg bid</td>
<td>Placebo</td>
<td>16 weeks</td>
<td>Chinese, Indians, Koreans</td>
<td>466</td>
<td>-1.2</td>
<td>-0.8</td>
<td>-1.3</td>
<td>-1.2</td>
<td>NA</td>
<td>NA</td>
<td>Nausea, vomiting, nasopharyngitis, diarrhea, anorexia, abdominal distention, pyrexia, dyspepsia arthralgia</td>
</tr>
<tr>
<td>Kadowaki 2009</td>
<td>Add on to SU alone, SU + BG or SU + TZD</td>
<td>randomized, single blind, placebo-controlled</td>
<td>Exenatide 2.5 μg bid; Exenatide 5 μg bid; Exenatide 10 μg bid</td>
<td>Placebo</td>
<td>12 weeks</td>
<td>Japanese</td>
<td>153</td>
<td>-0.9</td>
<td>-0.92</td>
<td>-1.86</td>
<td>+0.05</td>
<td>-0.92</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Iwamoto 2009</td>
<td>Add on to diet or exercise alone or in combination with a stable regimen of BG, SU, TZD, BG + SU, BG + TZD</td>
<td>randomized, double blind, placebo-controlled</td>
<td>exenatide 0.8 mg qw; exenatide 20 mg qw</td>
<td>Placebo</td>
<td>10 weeks</td>
<td>Japanese</td>
<td>30</td>
<td>-1.0</td>
<td>-0.6</td>
<td>-2.5</td>
<td>-0.6</td>
<td>0.05</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Liraglutide</strong></td>
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<tr>
<td>Seino 2008</td>
<td>Add on to diet with or without OAD</td>
<td>randomized, double blind, placebo-controlled</td>
<td>Liraglutide 0.1 mg qd; Liraglutide 0.3 mg qd; Liraglutide 0.6 mg qd; Liraglutide 0.9 mg qd</td>
<td>Placebo</td>
<td>14 weeks</td>
<td>Japanese</td>
<td>226</td>
<td>-0.72</td>
<td>-0.79</td>
<td>-1</td>
<td>0.05</td>
<td>0.14</td>
<td>8.2</td>
<td>infections and gastrointestinal disorders</td>
</tr>
<tr>
<td>Seino 2009a</td>
<td>Monotherapy</td>
<td>randomized, double blind, placebo-controlled</td>
<td>Liraglutide 0.9 mg/day</td>
<td>Glibenclamide 1.25 – 2.5 mg/day</td>
<td>24 weeks</td>
<td>Japanese</td>
<td>400</td>
<td>-1.74</td>
<td>-0.56</td>
<td>NA</td>
<td>-2.34</td>
<td>NA</td>
<td>diarrhea</td>
<td></td>
</tr>
<tr>
<td>Seino 2009b</td>
<td>Combination with SU</td>
<td>randomized, double blind, placebo-controlled</td>
<td>Liraglutide 0.6 mg/day; Liraglutide 0.9 mg/day</td>
<td>SU monotherapy</td>
<td>24 weeks</td>
<td>Japanese</td>
<td>264</td>
<td>-1.09</td>
<td>-1.15</td>
<td>-1.36</td>
<td>NA</td>
<td>neutral</td>
<td>-0.92</td>
<td>NA</td>
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</table>
### Sitagliptin

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Drug</th>
<th>Comparator</th>
<th>Duration</th>
<th>Region</th>
<th>Patients</th>
<th>HbA1c Changes</th>
<th>A1c Changes</th>
<th>SWT</th>
<th>NVT</th>
<th>Other Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iwamoto 2007</td>
<td>Monotherapy</td>
<td>Sitagliptin 25 mg qd, Sitagliptin 50 mg qd, Sitagliptin 100 mg qd, Sitagliptin 200 mg qd</td>
<td>Placebo</td>
<td>12 weeks</td>
<td>Japanese</td>
<td>363</td>
<td>-0.69/-0.41/-0.5</td>
<td>-1.05/-0.71/-0.8</td>
<td>neutral</td>
<td>NA</td>
<td>constipation, nasopharyngitis, pharyngitis, upper respiratory tract inflammation</td>
</tr>
<tr>
<td>Kadowaki 2008</td>
<td>Add on to metformin</td>
<td>Sitagliptin 50 mg qd</td>
<td>Placebo</td>
<td>12 weeks</td>
<td>Japanese</td>
<td>149</td>
<td>-0.7</td>
<td>-1.0</td>
<td>-0.42</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mohan 2009</td>
<td>Monotherapy</td>
<td>Sitagliptin 100 mg qd</td>
<td>Placebo</td>
<td>18 weeks</td>
<td>Indian, Korean</td>
<td>530</td>
<td>-0.7</td>
<td>-1.0</td>
<td>NA</td>
<td>-0.4</td>
<td>8.0</td>
</tr>
<tr>
<td>Chan 2008</td>
<td>Monotherapy</td>
<td>Sitagliptin 50 mg qd</td>
<td>Placebo</td>
<td>12 weeks DB + 40 weeks active treatment</td>
<td>Chinese</td>
<td>91</td>
<td>-0.6</td>
<td>-0.5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Maegawa 2008</td>
<td>Add on to pioglitazone</td>
<td>Sitagliptin 50 mg qd (could be titrated to 100 mg qd)</td>
<td>Placebo</td>
<td>12 weeks DB + 40 weeks active treatment</td>
<td>Japanese</td>
<td>134</td>
<td>-0.4</td>
<td>-0.8</td>
<td>-0.7</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Noro 2008</td>
<td>Monotherapy</td>
<td>Sitagliptin 100 mg qd</td>
<td>Placebo</td>
<td>12 weeks</td>
<td>Japanese</td>
<td>151</td>
<td>-0.65</td>
<td>-1.05</td>
<td>-1.25</td>
<td>-0.1</td>
<td>-0.15</td>
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<tr>
<td>NCT0041155 4</td>
<td>Monotherapy</td>
<td>Voglibose 0.2 mg tid</td>
<td>Placebo</td>
<td>12 weeks</td>
<td>Japanese</td>
<td>319</td>
<td>-0.7</td>
<td>-0.39</td>
<td>-1.1</td>
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### Vildagliptin

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Drug</th>
<th>Comparator</th>
<th>Duration</th>
<th>Region</th>
<th>Patients</th>
<th>HbA1c Changes</th>
<th>A1c Changes</th>
<th>SWT</th>
<th>NVT</th>
<th>Other Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kikuchi 2009</td>
<td>Monotherapy</td>
<td>Vildagliptin 10 mg bid, Vildagliptin 25 mg bid, Vildagliptin 50 mg bid</td>
<td>Placebo</td>
<td>12 weeks</td>
<td>Japanese</td>
<td>291</td>
<td>-0.8</td>
<td>-1.0</td>
<td>-0.75</td>
<td>-0.91</td>
<td>8.2 (only in vilda 50 mg)</td>
</tr>
</tbody>
</table>

SU = sulfonylurea, BG = biguanide, TZD = thiazolidinedione, OAD = oral antidiabetics, qd = once daily, bid = twice daily, tid = three times daily, DB = double-blind, NA = not available
DISCUSSION

The population in the included studies is generally less obese (typical BMI of 23 – 25 kg/m²) compared to the studies in Caucasian population (BMI of 29 – 35 kg/m²). Lack of effect on body weight with exenatide and liraglutide but not with sitagliptin and vildagliptin. Lack of effect on body weight and the lower initial levels of insulin resistance in the Asian subjects might explain the small improvement in HOMA-IR observed the above studies.

As expected, β-cell function (HOMA-β) was improved by all incretin-based therapies, but only in higher dose. This is also consistent with findings in Caucasian studies.

The safety profiles observed in the above studies were consistent with previous reports of incretin-based therapies for Caucasian populations, which are predominantly gastrointestinal in nature. No new safety issues were raised from the 14 studies.

Except for exenatide, the incidences of hypoglycemia with incretin-based therapies are generally low. Exenatide enhances insulin secretion from pancreatic β-cells in a glucose-dependent fashion, wherein insulin secretion decreases as glucose levels normalize. This mechanism reduces exenatide’s potential to cause hypoglycemia. However, as observed in DeFronzo and Kendall studies, dose-dependent increase in the incidence of hypoglycemia was also seen in Asian studies.

Incretin-based therapies are a relatively new option for the treatment of patients with type 2 diabetes. These agents hold promise in overcoming the limitations of traditional treatments which are typically associated with weight gain and associated hypoglycemia. The evidences on the efficacy and safety of incretin-based therapies in Asian population so far were encouraging, but many problems still need to be addressed. The majority of the above studies are trials evaluating efficacy of incretin-based therapies versus placebo. Many clinical trials comparing the efficacy of incretin-based therapy versus active control in Asian population are still ongoing. The longest trials available now are up to 52 weeks which provide only a safety profile up to 1 year and sustained efficacy on glycemic parameters. Long-term trials with hard cardiovascular endpoints in Asian type 2 diabetes are still needed. The reasons of the ethnic difference on the response in incretin treatments also remain to be clarified. Global trials with subgroup analysis on ethnic differences might provide a better head to head comparison between races/ethnic groups.

In conclusion, the magnitude of the effect of incretin-based therapies in Asian patients is relatively more pronounced on some glycemic parameters compared with those observed in Caucasian population. These clinical trial results indicate that GLP-1 agents may be more effective in Asian than in Caucasian populations.
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