To estimate the relative efficacy and tolerability of Type 2 Diabetes Mellitus: A Network Meta-analysis of Exenatide Once Weekly Plus Metformin for the Treatment of Type 2 Diabetes Mellitus


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Introduction

• Clinical guidelines in Europe, and the United States (US) recommend a step-wise, individualized approach to treatment of Type 2 diabetes mellitus (T2DM).
• The recommended sequence of treatment is 1) diet modifications and exercise; 2) addition of metformin (MET) monotherapy; 3) addition of other agents as needed to achieve glycaemic control, such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs). Exenatide is a GLP-1 RA approved for treatment of T2DM as a solution for twice-daily injection (BID, 5 or 10 µg) and as a prolonged-release once-weekly injection (QW, 2 µg), which contains the active ingredient of the exenatide BID formulation dispersed in microspheres in an aqueous formulation.
• There is a lack of head-to-head evidence to inform the efficacy and tolerability of exenatide QW relative to other GLP-1 RAs in the dual therapy setting.

Objective

• To estimate the relative efficacy and tolerability of exenatide 2 mg once-weekly (EQW), compared to other GLP-1 RAs for the treatment of adult patients with T2DM not adequately controlled on MET monotherapy.

Methods

• Systematic literature review (SLR) and network meta-analysis (NMA) of RCTs involving GLP-1 RAs approved in the US and/or Europe for the treatment of T2DM.
• MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched from inception to Oct 2014, and Pubmed from Aug to Oct 2014. Abstracts from two conferences (ADA 2013 / 2014 and EASD 2013) were hand-searched.
• Inclusion criteria: RCTs of ≤ 6 weeks duration, treatment with GLP-1 RA in T2DM patients with inadequately controlled HbA1c levels on MET monotherapy; ≥ 80% of patients in each treatment arm had to receive background MET monotherapy during the trial; and ≥ 80% must have had MET monotherapy or diet and exercise as the pre-trial diabetes management method.

Network meta-analysis

• A random effects (RE) model was chosen a priori. A fixed-effects (FE) model was to be selected over a RE model if it showed a significantly better fit to the data based on the Deviance Information Criterion or if there was large uncertainty around the posterior between-study variance under the RE model.
• The NMA was fitted by Markov Chain Monte Carlo techniques using the statistical package WinBUGS. Code was based on that recommended by the National Institute for Health and Clinical Excellence (NICE).
• The mean change in HbA1c was analyzed using the mean difference scale. Nausea as an adverse event (AE) and treatment discontinuation due to AEs were analyzed based on odds ratios.

Results

• 662 abstracts identified, 14 RCTs included.
• The NMA was informed by 14 trials for the HbA1c mean change from baseline network, 10 trials for the occurrence of nausea as an adverse event (AE) during treatment, and 13 trials for the proportion of patients discontinuing treatment due to AEs.
• RE models were used to estimate relative effect sizes for change in HbA1c and the occurrence of nausea. A FE model was used to evaluate effect sizes for the probability of treatment discontinuation due to AEs.
• All regimens performed better than placebo at reducing HbA1c levels when added to MET.
• There was a statistically non-significant trend of treatment discontinuation due to AEs.

Comparison of all treatment regimens with placebo

• Placebo plus MET was compared with all other treatment regimens in the network, for all endpoints of interest (Table 1).

Table 1. Relative effect sizes for change of HbA1c, risk of nausea and treatment discontinuation due to AEs, all GLP-1 RA treatments compared to placebo.

<table>
<thead>
<tr>
<th>Model type</th>
<th>Change in HbA1c from Baseline (%)</th>
<th>Risk of nausea</th>
<th>Risk of treatment discontinuation due to AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>EQW</td>
<td>0.69 (-1.11, -0.28)</td>
<td>23.74</td>
<td>29.00</td>
</tr>
<tr>
<td>Exenatide 5 µg BID</td>
<td>0.19 (0.17, 0.20)</td>
<td>2.07 (1.78, 97.61)</td>
<td>72.84</td>
</tr>
<tr>
<td>Liraglutide 1.2 mg QD</td>
<td>0.71 (-1.16, -0.26)</td>
<td>21.96</td>
<td>21.84</td>
</tr>
<tr>
<td>Lixisenatide 20 µg</td>
<td>0.75 (0.73, 0.77)</td>
<td>20.19</td>
<td>31.86</td>
</tr>
<tr>
<td>Dulaglutide 1.2 mg QD</td>
<td>0.82 (0.80, 0.84)</td>
<td>21.96</td>
<td>21.84</td>
</tr>
<tr>
<td>Liraglutide 1 mg QD</td>
<td>0.82 (0.80, 0.84)</td>
<td>21.96</td>
<td>21.84</td>
</tr>
</tbody>
</table>

Comparison of exenatide 2 mg QW with all other treatment regimens

• EQW obtained a statistically significant reduction in HbA1c relative to lixisenatide 20µg QD. Non-significant favorable point estimates were observed for EQW vs. albiglutide 30mg QW, exenatide 5 µg and 10 µg BID, and lixisenatide 2.4mg and 1.8mg QD (Fig 1A).
• EQW was associated with an equal or lower risk of nausea compared to all other GLP-1 RAs, except exenatide 5 µg BID. These differences did not reach statistical significance. (Fig 1B).
• The risk of treatment discontinuation due to AEs was lower for EQW than for dulaglutide 1.5mg QW, and lixisenatide 1.2mg and 1.8mg QD, and higher for EQW than for lixisenatide 20mg QD and exenatide 5 µg and 10 µg BID. None of these differences were statistically significant. (Fig 1C).

Conclusion

Exenatide QW is effective and has a similar tolerability profile, compared to other GLP-1 RAs, for the treatment of T2DM in adults inadequately controlled on metformin alone.