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ARTICLE

Subcutaneously administered tirzepatide vs semaglutide for adults with type 2 diabetes: a systematic review and network meta-analysis of randomised controlled trials

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Abstract

Aims/hypothesis We conducted a systematic review and network meta-analysis to compare the efficacy and safety of s.c. administered tirzepatide vs s.c. administered semaglutide for adults of both sexes with type 2 diabetes mellitus.

Methods We searched PubMed and Cochrane up to 11 November 2023 for RCTs with an intervention duration of at least 12 weeks assessing s.c. tirzepatide at maintenance doses of 5 mg, 10 mg or 15 mg once weekly, or s.c. semaglutide at maintenance doses of 0.5 mg, 1.0 mg or 2.0 mg once weekly, in adults with type 2 diabetes, regardless of background glucose-lowering treatment. Eligible trials compared any of the specified doses of tirzepatide and semaglutide against each other, placebo or other glucose-lowering drugs. Primary outcomes were changes in HbA_{1c} and body weight from baseline. Secondary outcomes were achievement of HbA_{1c} target of ≤48 mmol/mol (≤6.5%) or <53 mmol/mol (<7.0%), body weight loss of at least 10%, and safety outcomes including gastrointestinal adverse events and severe hypoglycaemia. We used version 2 of the Cochrane risk-of-bias tool (ROB 2) to assess the risk of bias, conducted frequentist random-effects network meta-analyses and evaluated confidence in effect estimates utilising the Confidence In Network Meta-Analysis (CINeMA) framework.

Results A total of 28 trials with 23,622 participants (44.2% female) were included. Compared with placebo, tirzepatide 15 mg was the most efficacious treatment in reducing HbA_{1c} (mean difference −21.61 mmol/mol [−1.96%]) followed by tirzepatide 10 mg (−20.19 mmol/mol [−1.84%]), semaglutide 2.0 mg (−17.74 mmol/mol [−1.59%]), tirzepatide 5 mg (−17.60 mmol/mol [−1.60%]), semaglutide 1.0 mg (−15.25 mmol/mol [−1.39%]) and semaglutide 0.5 mg (−12.00 mmol/mol [−1.09%]). In between-drug comparisons, all tirzepatide doses were comparable with semaglutide 2.0 mg and superior to semaglutide 1.0 mg and 0.5 mg. Compared with placebo, tirzepatide was more efficacious than semaglutide for reducing body weight, with reductions ranging from 9.57 kg (tirzepatide 15 mg) to 5.27 kg (tirzepatide 5 mg). Semaglutide had a less pronounced effect, with reductions ranging from 4.97 kg (semaglutide 2.0 mg) to 2.52 kg (semaglutide 0.5 mg). In between-drug comparisons, tirzepatide 15 mg, 10 mg and 5 mg demonstrated greater efficacy than semaglutide 2.0 mg, 1.0 mg and 0.5 mg, respectively. Both drugs increased incidence of gastrointestinal adverse events compared with placebo, while neither tirzepatide nor semaglutide increased the risk of serious adverse events or severe hypoglycaemia.

Conclusions/interpretation Our data show that s.c. tirzepatide had a more pronounced effect on HbA_{1c} and weight reduction compared with s.c. semaglutide in people with type 2 diabetes. Both drugs, particularly higher doses of tirzepatide, increased gastrointestinal adverse events.

Registration PROSPERO registration no. CRD42022382594

Keywords GIP/GLP-1 receptor agonist · GLP-1 receptor agonist · Network meta-analysis · Semaglutide · Systematic review · Tirzepatide

Abbreviations

CINeMA	Confidence In Network Meta-Analysis
EMA	European Medicines Agency
FDA	US Food and Drug Administration
GIP	Glucose-dependent insulinotropic peptide
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
MD	Mean difference

Extended author information available on the last page of the article

Research in context

What is already known about this subject?

- Semaglutide and tirzepatide, administered s.c., have a well-established effect in lowering glucose levels and body weight in individuals with type 2 diabetes
- There are only two RCTs directly comparing these two medications

What is the key question?

- How do s.c. tirzepatide and s.c. semaglutide compare in terms of efficacy and safety for treating type 2 diabetes?

What are the new findings?

- All three tirzepatide doses investigated (15 mg, 10 mg and 5 mg) were comparable with semaglutide 2.0 mg and superior to semaglutide 1.0 mg and 0.5 mg in reducing HbA_{1c}
- Tirzepatide 15 mg, 10 mg and 5 mg demonstrated greater efficacy in reducing weight than semaglutide 2.0 mg, 1.0 mg and 0.5 mg, respectively
- Both drugs, particularly tirzepatide 15 mg, increased incidence of gastrointestinal adverse events compared with placebo

How might this impact on clinical practice in the foreseeable future?

- Our findings indicate that s.c. tirzepatide may be a preferable treatment option to s.c. semaglutide for people with type 2 diabetes when glycaemic control and weight reduction are primary treatment goals

Introduction

Semaglutide, administered s.c., has shown superior efficacy compared with other glucose-lowering agents, including its oral formulation, in reducing HbA_{1c} and in facilitating weight loss in individuals with type 2 diabetes [1, 2]. Initially approved at doses of 0.5 mg and 1.0 mg once weekly, it has subsequently received authorisation for a 2.0 mg once-weekly dose for the management of type 2 diabetes. Tirzepatide, a novel agent belonging to the glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 receptor agonist (GLP-1 RA) class (dual GIP/GLP-1 RA), has also been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of type 2 diabetes. Data from RCTs have consistently shown the efficacy of tirzepatide in reducing HbA_{1c} and body weight in people with type 2 diabetes [3].

The ADA Standards of Care and the ADA/EASD consensus report recommend s.c. administered semaglutide and tirzepatide as the most efficacious medications for glycaemic control (alongside dulaglutide) and weight reduction [4, 5]. However, direct comparison between s.c. tirzepatide and s.c. semaglutide in RCTs is scarce [6, 7], presenting a challenge in drawing robust and precise conclusions regarding their comparative efficacy. To address this research gap, we conducted a network meta-analysis utilising both direct and indirect comparative data between the two medications [8].

The aim of our systematic review and network meta-analysis was to compare the efficacy (in terms of glycaemic control and weight management) and safety (in terms of adverse events) of s.c. tirzepatide and s.c. semaglutide in people with type 2 diabetes based on data from RCTs.

Methods

The protocol of this systematic review and meta-analysis is registered in PROSPERO (registration no. CRD42022382594) [9]. We report our methods and results in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement for network meta-analyses [10].

Eligibility criteria We included RCTs published in English that assessed s.c. tirzepatide at maintenance doses of 5 mg, 10 mg or 15 mg once weekly, or s.c. semaglutide at maintenance doses of 0.5 mg, 1.0 mg or 2.0 mg once weekly for a minimum duration of 12 weeks. Eligible trials compared any of the specified doses of tirzepatide and semaglutide against each other, placebo or other glucose-lowering drugs.

For a glucose-lowering drug to be included as a comparator, it was required to have been evaluated in at least one trial comparison against tirzepatide and one trial comparison against semaglutide. This approach was adopted to prevent unconnected networks, ensuring that each comparator served as a link for indirect comparisons between tirzepatide and semaglutide. We included trials recruiting adults with type 2 diabetes regardless of their background glucose-lowering treatment, defined as the glucose-lowering therapy used both in the intervention and control arms after the randomisation.

Information sources and searches We searched PubMed and Cochrane databases from inception until 11 November 2023. Our search strategy included both free-text and Medical Subject Headings (MeSH) terms, utilising the keywords 'tirzepatide,' 'ly3298176,' 'semaglutide' and 'nn9535' (electronic supplementary material [ESM] Table 1).

Study selection After deduplication, search results were screened at title and abstract level, and potentially eligible records were examined in full text with reasons for exclusion being recorded. Two independent reviewers performed the study selection process and any disagreements were resolved by a third reviewer. For the deduplication and the screening process we used the Systematic Review Accelerator (SRA) web application [11].

Data collection Using predesigned forms, we extracted information on study characteristics, participants' baseline characteristics and outcome data. Given the aggregated data format of the included RCTs in our meta-analysis, direct information on how sex or gender was determined in the individual studies was beyond the scope of our analysis. Our two primary outcomes were the change from baseline in HbA_{1c} and in body weight. Secondary efficacy outcomes were the proportion of participants attaining an HbA_{1c} target of ≤48 mmol/mol (≤6.5%) or <53 mmol/mol (<7.0%), and those achieving a minimum of 10% body weight loss. Safety outcomes included the incidence (no. of participants with at least one outcome event) of nausea, vomiting, diarrhoea, treatment discontinuation due to gastrointestinal events, severe adverse events and severe hypoglycaemia (a hypoglycaemic event requiring assistance). Data were extracted from the intention-to-treat population, which included all randomly assigned participants who received at least one dose of the study medication. For eligible trials identified through our database searches, we utilised ClinicalTrials.gov, using their respective National Clinical Trial (NCT) identifiers, to retrieve additional information when outcome data were absent or incomplete in the published articles. Data extraction was conducted by two independent reviewers, with discrepancies resolved by a third reviewer.

Risk-of-bias assessment We used version 2 of the Cochrane risk-of-bias tool for randomised trials (ROB 2) to assess the risk of bias for the two primary outcomes [12]. Following the tool's algorithms, each trial's overall risk of bias was classified as low if all domains were at low risk, and high if any domain was at high risk. If none of the domains were classified as high risk but one or more were deemed to have some concerns, the overall risk of bias for that trial was categorised as 'of some concern'. This assessment was conducted independently by two reviewers, with a third reviewer resolving any disagreements. We evaluated the presence of small-study effect (publication bias) by means of comparison-adjusted funnel plots [13].

Data analysis We explored the transitivity assumption by comparing the distribution of potential effect modifiers (baseline HbA_{1c} and body weight) across treatment comparisons [14]. We conducted frequentist random-effects network meta-analyses and calculated mean differences (MDs) for the two primary outcomes and risk ratios for dichotomous outcomes, alongside 95% CIs [15]. We evaluated heterogeneity for the primary outcomes based on the agreement between CIs and prediction intervals in relation to the null effect and the clinically important effect on the opposite direction to the point estimate [16, 17]. We assumed a minimum reduction in HbA_{1c} of 5.5 mmol/mol (0.5%) and in body weight of 4.5 kg (5% of mean body weight value at baseline across all trials) as clinically important [18]. We addressed incoherence (inconsistency) both locally by comparing directly with indirect evidence using the Separating Indirect from Direct Evidence (SIDE) method [19] and globally using the design-by-treatment interaction model [20]. Moreover, we used P-scores, ranging from 0 to 1, to rank treatments; these can be interpreted as the average degree of certainty for a treatment to be better than the other treatments in the network [21]. Statistical analyses were performed in R (R Core Team 2019, R Foundation for Statistical Computing, Vienna, Austria) using the R packages 'meta' and 'netmeta' [22], and in NMAstudio (version 2.0) web application [23, 24].

Evaluation of confidence in findings We evaluated Confidence In Network Meta-Analysis (CINeMA) effect estimates for the primary outcomes utilising the CINeMA methodological framework and application [17, 25]. The six domains evaluated were within-study bias (risk of bias), across-study bias (small-study effect/publication bias), indirectness, imprecision, heterogeneity and incoherence (inconsistency). We assigned judgements at three levels (no concerns, some concerns and major concerns) to each domain and summarised judgements across domains to an overall assessment ranging across very low, low, moderate or high level of confidence [17, 25].

Results

Search results and study characteristics The search retrieved 2798 records, of which 28 RCTs [6, 7, 26–51] with 23,622 participants were included in the systematic review and network meta-analysis (ESM Fig. 1). Study and participant characteristics are presented in Table 1. Only two trials directly compared tirzepatide with semaglutide, with one of these also including a placebo arm [6, 7]. Sixteen trials compared semaglutide with placebo, other GLP-1 RAs, basal insulin, prandial insulin or varying doses of semaglutide. The remaining ten trials compared tirzepatide with placebo, GLP-1 RA (other than semaglutide), basal insulin, prandial insulin or varying doses of tirzepatide. All trials had a parallel-group design and 15 were open-label (Table 1). Most trials were multinational, except for five that recruited exclusively Japanese participants [39–41, 48, 49]. The intervention duration ranged from 24 to 28 weeks in five trials and from 30 to 56 weeks in 21 trials. The remaining two trials, a trial with tirzepatide in people with obesity and type 2 diabetes (SURMOUNT-2) [50] and a cardiovascular outcomes trial with semaglutide (SUSTAIN 6) [31], had a duration of 72 and 104 weeks, respectively. The background glucose-lowering therapy, referring to the common treatment received by all trial groups post-randomisation, varied across the trials. However, the predominant background treatment was metformin, used either as monotherapy or in combination with other medications. Across all trials, 10,442 participants (44.2%) were female, participants' mean HbA_{1c} at baseline was 66.6 mmol/mol (8.3%), mean body weight was 88.8 kg and mean age was 57.8 years (Table 1). The distribution of potential effect modifiers (HbA_{1c} and body weight at baseline) was deemed sufficiently similar across all treatment comparisons to assume that a network meta-analysis was appropriate (ESM Figs 2 and 3).

Overview of network Figure 1 shows the network of comparisons used in the meta-analysis. Risk of bias for the change in HbA_{1c} was assessed as low in all trials except for one that was at high risk of bias and one with some concerns (ESM Table 2). For the change in body weight, seven trials were at high risk of bias and one trial had some concerns; all other trials were at low risk of bias (ESM Table 3). Comparison-adjusted funnel plots did not suggest the presence of small-study effect (ESM Figs 4 and 5). There was presence of heterogeneity in some comparisons, particularly those involving semaglutide 2.0 mg (ESM Tables 4 and 5). In terms of incoherence, the design-by-treatment interaction model did not identify global inconsistency in the analyses for both primary outcomes (ESM Tables 4 and 5), while local inconsistency was also low.

Glycaemic efficacy Compared with placebo, tirzepatide 15 mg was the most efficacious treatment in reducing HbA_{1c} (MD [95% CI]: −21.61 mmol/mol [−23.26 to −19.97] [−1.96% (−2.11 to −1.82)]), followed by tirzepatide 10 mg (−20.19 mmol/mol [−21.89 to −18.48] [−1.84% (−1.99 to −1.69)]), semaglutide 2.0 mg (−17.74 mmol/mol [−22.03 to −13.45] [−1.59% (−1.95 to −1.22)]), tirzepatide 5 mg (−17.60 mmol/mol [−19.36 to −15.84] [−1.60% (−1.75 to −1.44)]), semaglutide 1.0 mg (−15.25 mmol/mol [−16.73 to −13.77] [−1.39% (−1.52 to −1.26)]) and semaglutide 0.5 mg (−12.00 mmol/mol [−13.74 to −10.26] [−1.09% (−1.24 to −0.94)]) (Fig. 2 and ESM Fig. 6). In comparisons between tirzepatide and semaglutide, when HbA_{1c} was measured in mmol/mol, all tirzepatide doses were comparable with semaglutide 2.0 mg and superior to semaglutide 1.0 mg and 0.5 mg (ESM Table 6). Specifically, effect estimates (MD [95% CI]) for tirzepatide 15 mg vs semaglutide 2.0 mg, tirzepatide 10 mg vs semaglutide 1.0 mg, and tirzepatide 5 mg vs semaglutide 0.5 mg were, respectively, as follows: −3.87 mmol/mol (−8.22 to 0.48); −4.94 (−6.65 to −3.23); and −5.60 mmol/mol (−7.60 to −3.60) (ESM Table 6). When HbA_{1c} was measured in %, tirzepatide at doses of 15 mg, 10 mg and 5 mg demonstrated greater efficacy than semaglutide at doses of 2.0 mg (MD = −0.38% [95% CI −0.75% to −0.01%]), 1.0 mg (MD = −0.45% [95% CI −0.60% to −0.31%]) and 0.5 mg (MD = −0.51% [95% CI −0.68% to −0.33%]), respectively (ESM Table 7). The confidence in estimates for comparisons between tirzepatide and semaglutide was high to moderate, except for comparisons vs semaglutide 2.0 mg, where the confidence was generally low (ESM Table 8). Consistently with meta-analysis findings, tirzepatide 15 mg held the highest probability (P-score = 0.99) of being the most efficacious treatment in reducing HbA_{1c} (ESM Fig. 7).

Compared with placebo, semaglutide 2.0 mg (risk ratio = 7.73 [95% CI 5.62, 10.63]) and tirzepatide 15 mg (risk ratio = 7.01 [95% CI 5.73, 8.57]) were the most efficacious in achieving an HbA_{1c} target of ≤48 mmol/mol (≤6.5%) (ESM Table 9). In between-drug comparisons, tirzepatide 15 mg and 10 mg outperformed semaglutide 1.0 mg and 0.5 mg and tirzepatide 5 mg was superior to semaglutide 0.5 mg, while no differences were found between semaglutide 2.0 mg and any of the tirzepatide doses (ESM Table 9). Similarly, semaglutide 2.0 mg (risk ratio = 4.01 [95% CI 3.24, 4.95]) and tirzepatide 15 mg (risk ratio = 3.70 [95% CI 3.26, 4.20]) were the most efficacious in achieving an HbA_{1c} target of <53 mmol/mol (<7%) as compared with placebo (ESM Table 10). No differences were found when any of the tirzepatide doses were compared with semaglutide 2.0 mg or 1.0 mg, while all tirzepatide doses were superior to semaglutide 0.5 mg (ESM Table 10).

Table 1 Study details and participant baseline characteristics of included arms in RCTs

Study (trial registration no.)/ study arm	Study duration, weeks	Blinding status	Background glucose-lowering therapy[a]	Participants randomised, *n*	Female sex, *n*	Mean HbA_{1c}, mmol/mol	Mean HbA_{1c}, %	Mean body weight, kg	Mean diabetes duration, years	Mean age, years
SUSTAIN 1 [26] (NCT02054897)	30	Double-blind	None							
Semaglutide 0.5 mg				128	68	64.9	8.1	89.8	4.8	54.6
Semaglutide 1.0 mg				130	50	65.3	8.1	96.9	3.6	52.7
Placebo				129	59	63.4	8.0	89.1	4.1	53.9
SUSTAIN 2 [27] (NCT01930188)	56	Double-blind	Metformin monotherapy (55%) or metformin+TZD (45%)							
Semaglutide 0.5 mg				409	202	64.1	8.0	89.9	6.4	54.8
Semaglutide 1.0 mg				409	204	64.4	8.0	89.2	6.7	56.0
SUSTAIN 3 [28] (NCT01885208)	56	Open-label	Monotherapy or dual combination with metformin (96.5%)/sulfonylurea (48.1%)/TZDs (2.3%)							
Semaglutide 1.0 mg				404	185	67.9	8.4	96.2	9.0	56.4
GLP-1 RA (exenatide extended release)				405	177	67.6	8.3	95.4	9.4	56.7
SUSTAIN 4 [29] (NCT02128932)	30	Open-label	Metformin monotherapy (48%) or metformin+sulfonylurea (52%)							
Semaglutide 0.5 mg				362	165	65.4	8.1	93.7	7.8	56.5
Semaglutide 1.0 mg				360	178	66.6	8.3	94.0	9.3	56.7
Basal insulin (glargine)				360	165	65.4	8.1	92.6	8.6	56.2
SUSTAIN 5 [30] (NCT02305381)	30	Double-blind	Basal insulin monotherapy (16.7%) or basal insulin+metformin (83.3%)							
Semaglutide 0.5 mg				132	58	67.9	8.4	92.7	12.9	59.1
Semaglutide 1 mg				131	54	67.3	8.3	92.5	13.7	58.5
Placebo				133	62	68.6	8.4	89.9	13.3	58.8
SUSTAIN 6 [31] (NCT01720446)	104	Double-blind	None, or monotherapy/ dual-combination therapy with any glucose-lowering medication							
Semaglutide 0.5 mg				826	331	71.6	8.7	91.8	14.3	64.6
Semaglutide 1.0 mg				822	304	71.6	8.7	92.9	14.1	64.7

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