AMJ Australasian Medical Journal [AMJ 2020;13(9):262-266]

Oral semaglutide adequate glycaemia control with safe cardiovascular profile: Systematic review

Abdulaziz Abdulrahman A. Bedaiwi[1], Marwan Fahad H Altemani[1], Nadia Abdullah M Alzahrani[1], Ali Khaled A Alghannami[1], Maram Ali S Jarallah[1], Razan Faisal M Aljohani[1], Fahad Saad M Alsuhaymi[1], Sultan Abdullah M. Alamri[1], Saud Abdulrahman S Alghamdi[1], Wasan Suwailem S Albalawi[1], Abdulelah Hamdan K Alonizei[1], Abdulmajeed Faisal A Albalawi[1], Mohammed Saad M Alnawmasi[1], Omniyyah Ahmed Alnahyah[1], Rawabi Talal S Aljayani[1], Ibrahim Mahmoud Ajwah[2], and Hazem Radi Rayyan[3]

1. University of Tabuk, Saudi Arabia
2. King Salman Armed Forced Hospital, Tabuk, Saudi Arabia
3. Department of Internal Medicine and Endocrinology, King Salman Armed Forced Hospital, Tabuk, Saudi Arabia

RESEARCH

Please site this paper as: Bedaiwi A, Altemani M, Alzahrani N, Alghannami A, Jarallah M, Aljohani R, Alsuhaymi F,Alamri S, Alghamdi S, Albalawi W, Alonizei A, Albalawi A, Alnawmasi M, Alnahyah O, Aljayani R, Ajwah I, Rayyan H. Oral semaglutide adequate glycemic control with safe cardiovascular profile: Systematic review. AMJ 2020;13(9):262–266.
https://doi.org/10.35841/1836-1935.13.9.262-266

Corresponding Author:
Ibrahim Mahmoud Ajwah
King Salman Armed Forced Hospital PO Box 3458 Tabuk 51937, Saudi Arabia
Email: Aj.wa@hotmail.com

ABSTRACT

Background
Type 2 diabetes is a chronic and progressive disease that associated with series complication such as major adverse cardiovascular events. Adequate glycaemic control proven to reduce this risk. Orally administered semaglutide promising medication in managing patient with type 2 diabetes.

Aims
To assess the cardiovascular safety and efficacy of semaglutide, a recently approved glucagon-like peptide 1 receptor agonist (GLP-1 RA) for type 2 diabetes.

Methods
Pub Med, Google Scholar, and EBSCO databases were systematically search for relevant articles. The terms diabetes, Glucagon-like peptide, semaglutide were used. Out of hundred twenty-two records, only four fulfilled the inclusion criteria.

Results
Four placebo-controlled studies with oral semaglutide were included. Single study concern about the cardiovascular safety of oral semaglutide and showed that, compared with placebo, semaglutide was not associated with increased in the cardiovascular events. On the other hand, the remaining trials shown that, semaglutide can effectively control the blood glucose as evident by reduction in HA1c.

Conclusion
Oral semaglutide can effectively and safely lower blood glucose without increase in the major adverse cardiovascular events (MACE).

Key Words
Semaglutide, GLP-1, diabetes

What this study adds:

1. What is known about this subject?
For patients with type 2 diabetes, Injectable semaglutide, indicated for both diquat glycaemic control as well as to reduce risk of major adverse cardiovascular events (MACE).

2. What new information is offered in this study?
In uncontrolled diabetes, despite optimum life style modification and metformin dose, glucagon-like peptide 1

receptor agonist in form of oral semaglutide, provide additional effective and safe treatment choice.

3. What are the implications for research, policy, or practice?

The current study show that, oral semaglutide at dose of 14 mg resulted in strong reduction in HA1c, without significant increase in major adverse cardiovascular events (MACE).

Background

Type 2 diabetes (T2D) is a chronic and progressive metabolic disorder characterised by peripheral insulin resistance and β-cell defect leading to insulin deficiency.[1]

Insulin secretagogues such as sulfonylurea (SU) and meglitinide analogues medications were the first therapies for β-cell defect and insufficient insulin secretion, these drugs enhance insulin secretion independently of blood glucose level which put the patients at a risk of hypoglycaemia. Furthermore, as derived from the U.K. Perspective Diabetes Study, the ability of SU to stimulate insulin secretion diminished with the passage of the time as an indicator of deterioration in β-cell function.[2,3]

Glucagon-like peptide (GLP-1) hormone stimulates the insulin secretion in glucose-dependent manner, inhibit glucagon secretion and expand β-cell. Subcutaneous semaglutide is an example of glucagon-like peptide 1 receptor agonist (GLP-1RA) that approved by the U.S. Food and Drug Administration (FDA) and currently recommended as second-line therapy for the management of type 2 diabetes mellitus.[4-6]

Recently, an oral form of semaglutide once-daily GLP-1 receptor agonist has been approved for treatment of patients with Type 2 diabetes (T2D). 7 The current review aimed to summarize the major randomized controlled trials that examine oral semaglutide for it is glycaemia controlefficacy and cardiovascular safety.

Method

A systematic electronic search was conducted including the Pub Med, Google Scholar, and EBSCO using the following terms in different combinations diabetes, Glucagon-like peptide, semaglutide. A full text randomized controlled trials that available in English, aimed to assess the role of oral semaglutide for it is efficacy and safety were included. Studies published in abstract form only were excluded. The abstracts and full texts were screened independently by two authors (AI, AB). The authors extracted the data, and then the author's names, year and region of publication, the study type, period of study, and the result were reported (Table1). The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Chart was used in the current survey (Figure 1).

Results

The initial literature search resulted in 122 records, after duplicates were removed and applying the inclusion criteria only four randomized control trials aimed to compered oral semaglutide with placebo were included in the current review. A total of 4949 patients were included. The studies duration was ranged between 26–52 weeks. [8-11] Once-daily oral semaglutide 14mg, were used in 3 out of 4 trials.[8-10] While a single trial compared three different dosage of semaglutide (3, 7 and 14mg) with placebo.[11] First trial, aimed to establish the cardiovascular safety of oral semaglutide, 3183 patients were randomized in 1:1 ratio to either, 14 mg once daily semaglutide or placebo, at the end of trial, Husain and collage conclude the non inferiority of oral semaglutide in comparison with placebo.[8] Mosenzon et al. conduct a phase 3 randomized, placebo-controlled, double-blind trials. The change from baseline HA1c was the primary end-point of the study. At week 26 oral semaglutide successfully reduce the HA1c by 1 per cent.[9]

To evaluate the change from baseline to week 26 in HbA1c, seven hundred and eleven diabetic patients with HbA1c of 7·0–9·5 per cent were participate in a Phase 3 randomized, placebo-controlled, double-blind trials, and randomly assigned (2:2:1) to oral semaglutide, subcutaneous liraglutide, or placebo once daily. At week 26, those who receive oral semaglutide successfully achieved 1.2 per cent reduction in HA1c.[10]

The last trial, was a randomized, double-blind, placebo controlled, parallel-group trial, included 731 patients with uncontrolled type 2 diabetes on insulin, participants were randomized to oral semaglutide 3mg, 7mg, or 14mg or to placebo. At week 26 oral semaglutide was superior to placebo in reducing HbA1c (–0.5 per cent, –0.9 per cent, and –1.2 per cent) for 3, 7, and 14 mg, respectively.[11]

Discussion

The current review summarizes the major trials that examine the first orally administrated GLP-1 receptor agonist that approved for the treatment of type 2 diabetes. [12]

Atherosclerotic cardiovascular disease (ASCVD) in form of coronary heart disease, cerebrovascular disease and

peripheral arterial disease, considered the leading cause of death among patients with diabetes. Furthermore, individuals with diabetic at greater risk (up to 50 per cent) increase in cardiovascular related death. [13,14]

Despite the association between the adequate glycemic control and improve the cardiovascular outcome, trials, such as ACCORD trial [15] and UGDP [16] raise the concern of the effect of antidiabetic medication on the cardiovascular risk. Compared with placebo, oral semaglutide provide effective glycaemic control with non-significant increase in the major adverse cardiovascular events (MACE) as shown in PIONEER 6 trial.[8]

The efficacy of oral semaglutide (14mg) was assessed in two trials, Mosenzon et al., Pratley et al., respectively. Both studies confirm the superiority of oral semaglutide over placebo as evident by significantly higher HA1c reduction.[9,10]

The dose dependent effect of semaglutide was examined in randomized, double-blind, placebo controlled, parallel-group trial. Where the participant assigned to receive semaglutide in three different strength, the maximum HA1c reduction was observed among those who assigned to semaglutide 14mg.[11]

Conclusion

Compared with placebo, oral semaglutide can effectively and safely lower blood glucose without increase in the major adverse cardiovascular events (MACE).

References

1. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature. 2001;414:799–806.
2. Raptis SA, Dimitriadis GD. Oral hypoglycemic agents: insulin secretagogues, alpha-glucosidase inhibitors and insulin sensitizers. Exp Clin Endocrinol Diabetes. 2001;109(Suppl. 2):S265–S287.
3. Turner RC. The U.K. Prospective Diabetes Study: a review. Diabetes Care. 1998;21(Suppl. 3):C35–C38.
4. Edvell A, Lindstrom P. Initiation of increased pancreatic islet growth in young normoglycemic mice (Umea). Endocrinology. 1999;140:778–783.
5. Food and Drug Administration (FDA). OZEMPIC (semaglutide) injection, for subcutaneous use. Initial U.S. Approval: 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209637lbl.pdf Accessed: January 15, 2018
6. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018;41:2669–2701.
7. Rybelsus® (semaglutide tablets), the first GLP-1 in a tablet approved in the US. https://www.novonordisk.com/media/news-details.2172050.html. Accessed September 23, 2019.
8. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019;381:841–851.
9. Mosenzon O, Blicher TM, Rosenlund S, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial. Lancet Diabetes Endocrinol. 2019;7:515–527.
10. Pratley R, Amod A, Hoff ST, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. Lancet. 2019;394:39–50.
11. Zinman B, Aroda VR, Buse JB, et al. Efficacy, Safety and Tolerability of Oral Semaglutide Versus Placebo Added to Insulin ± Metformin in Patients with Type 2 Diabetes: the PIONEER 8 Trial. [published online ahead of print September 17, 2019]. Diabetes Care. doi: 10.2337/dc19-0898.
12. Rybelsus® (semaglutide tablets), the first GLP-1 in a tablet approved in the US. https://www.novonordisk.com/media/news-details.2172050.html. Accessed September 23, 2019.
13. ADA 9. Cardiovascular disease and risk management: standards of medical care in diabetes—2018. Diabetes Care. 2018;41(1):S86–S104.
14. Sharma A, Green JB, Dunning A, et al. Causes of death in a contemporary cohort of patients with type 2 diabetes and atherosclerotic cardiovascular disease: insights from the TECOS trial. Diabetes Care. 2017;40(12):1763–1770. doi: 10.2337/dc17-1091.
15. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545–2559. doi: 10.1056/NEJMoa0802743.
16. Meinert CL. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. Diabetes. 1970;19:789–830.

PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

FUNDING

None

Table 1: RCTs that evaluated the effect of oral semaglutide

	Author–Year	Methods	Results
1	**Husain et al.**[8] **2019** **(PIONEER 6)**	Study design: Randomized, double-blind, placebo-controlled trial Treatment regimen: once-daily oral semaglutide (target dose, 14mg) or placebo Follow-up duration: 64 weeks Primary endpoint: cardiovascular outcome	Study Participants: 3183 Result: Major adverse cardiovascular events occurred in 61 of 1591 patients (3.8%) in the oral semaglutide group and 76 of 1592 (4.8%) in the placebo group Conclusion: The cardiovascular risk profile of oral semaglutide was not inferior to that of placebo
2	**Mosenzon et al.**[9] **2019** **(PIONEER 5)**	Study design: Phase 3 randomized, placebo-controlled, double-blind trials Treatment regimen: once-daily oral semaglutide (target dose, 14mg) or placebo Follow-up duration: 26 weeks Primary endpoint: Change in HA1c	Study Participants: 324 Result: Mean changes from baseline in HbA1c at week 26 were –1·0% for oral semaglutide and –0·2% for placebo Conclusion: Oral semaglutide was effective in patients with type 2 diabetes and moderate renal impairment
3	**Pratley et al.**[10] **2019** **(PIONEER 4)**	Study design: Phase 3 randomized, placebo-controlled, double-blind trials Treatment regimen: A)- once-daily oral semaglutide (dose escalated to 14mg) B)- once-daily subcutaneous liraglutide (dose escalated to 1·8mg) C)- placebo Follow-up duration: 52 weeks Primary endpoint: Change in HA1c	Study Participants: 711 Result: Mean change from baseline in HbA1c at week 26 was –1·2% with oral semaglutide, –1·1% with subcutaneous liraglutide, and –0·2% with placebo Conclusion: Oral semaglutide was non-inferior to subcutaneous liraglutide and superior to placebo in decreasing HbA1c
4	**Zinman et al.**[11] **2019** **(PIONEER 8)**	Study design: Randomized, double-blind, placebo controlled, parallel-group trial Treatment regimen: A)- oral semaglutide 3mg B)- oral semaglutide 7mg C)- oral semaglutide 14mg D)- Placebo Follow-up duration: 52 weeks Primary endpoint: Change in HA1c	Study Participants: 731 Result: Oral semaglutide was superior to placebo in reducing HbA1c (estimated treatment difference –0.5%, –0.9%, and –1.2% for 3, 7, and 14mg, respectively) Conclusion: Oral semaglutide was superior to placebo in reducing HbA1c

Figure 1: Flow diagram through the different phases of the systematic review (PRISMA flowchart)