



Editorial

EXENATIDE QW – NEW PERSPECTIVES 5 YEARS AFTER ITS FIRST USE

Cristian Guja , Andrada Mihai

National Institute of Diabetes, Nutrition and Metabolic Diseases “Prof. N.C. Paulescu”, Bucharest, Romania
University of Medicine and Pharmacy “Carol Davila”, Bucharest, Romania

received: November 16, 2017 accepted: December 02, 2017

available online: December 15, 2017

It already became a cliché to start a diabetes paper by reviewing epidemiological data and highlighting that this disease has become a global pandemic. However, the latest IDF data released in the form of the 8th edition of the Atlas [1] are worth mentioning. Thus, the estimated number of diabetes patients worldwide in 2017 is 425 million, expected to rise to 629 million patients by 2045, most of which are type 2 diabetes (T2DM) cases. More dramatic is the fact that all previous estimations have been largely surpassed by reality, diabetes prevalence already reaching the level predicted in the 4th edition of the Atlas (2009) for the year 2030. The good news is that improved care of diabetes subjects nowadays is already leading to a decrease in the rate of complications, including chronic kidney disease and cardiovascular disease (CVD) [2].

One may speculate that these improvements are obtained by the increased use of modern diabetes medications [3] which increase glycemic control with a lower risk of hypoglycemia. In fact, current treatment guidelines advocate the importance of minimizing the risk of hypoglycemia and weight gain [4], side effects not only associated with increased morbidity and mortality, but also

decreasing patient adherence and compliance. In fact poor medication adherence seems to explain why majority of patients still lack achievement of proposed glycemic targets [5]. The most efficient class of modern injectable non-insulin diabetes medications is represented by the glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) [6]. GLP-1RAs act by increasing insulin secretion and inhibiting glucagon production. In addition, they promote weight loss following stimulation of the hypothalamic satiety centers and prolongation of gastric emptying.

Exenatide was the first in class GLP-1RA, approved for T2DM treatment in 2005/2006. It is a synthetic derivative of exendin-4, a peptide identified initially in the saliva of the *Gila Monster* [7]. Exendin-4 contains 39 amino-acids and has a homology of 50% with the human GLP-1. Despite this rather low percentage, exendin-4 maintains full ability to bind to the human GLP-1 receptor. After subcutaneous injection of 5 µg, exenatide reaches a maximum serum concentration of 85 pg/mL and has a mean half-life of 2-to-3 hours [7,8]. This is why for clinical use exenatide is administered twice daily (BID) in a dosage of 5 µg or 10 µg. It is used either in monotherapy or in combination

✉ 5-7 Ion Movila Street, Bucharest 2, Romania. Tel: 0040212108499. Fax: 0040212102295
corresponding author e-mail: cristian.guja@b.astral.ro

with other diabetes drugs including oral antidiabetics (metformin, sulphonylureas, thiazolidindiones) or insulin in double or triple therapy. Randomized controlled studies showed that exenatide BID is associated with HbA1c reductions of around 1% and weight loss of approximately 2-3 kg [8]. Due to its short duration of action, exenatide BID has stronger effects on post-prandial blood glucose in comparison with longer acting GLP-1RAs [9].

Another exenatide formulation with extended release has been obtained by dispersing the drug in biodegradable microspheres made of a polymer proved to be safe for human use - poly(D,L-lactide-co-glycolide) [7,8]. The polymer degrades slowly over time and thus releases gradually exenatide in three stages [10]: initial release (2 days), slow diffusion (up to 14 days) and late release (up to 7 weeks). Thus, after once weekly subcutaneous injection of 2 mg exenatide, the drug is delivered from the injected microspheres constantly, reaching therapeutic plasma concentrations of around 50 pg/mL after 2 weeks of treatment [11] and a steady state plateau after around 6 weeks. The once weekly exenatide (ExQW) has been approved for human use in 2011 by the European Medicines Agency (EMA) and in 2012 by the Food and Drug Administration (FDA) in the USA and marketed under the trade name of Bydureon[®] both in Europe and the USA. At that time, it was (again) the first-in-class once weekly GLP-1RA. Initially, ExQW was injected using a syringe single tray system [8] and, since 2015, by an easy to use dual-chamber pen [12].

The efficacy and safety of ExQW was tested in a large phase 3 clinical trial program called DURATION (Diabetes therapy Utilization: Researching changes in A1C, weight, and other factors Through Intervention with exenatide ONce weekly) [8]. All these studies had a primary randomized phase with duration of 24 to

30 weeks. Some DURATION studies were designed to have open-label long-term extensions, the longest one being that of DURATION-1 (comparison of ExQW with exenatide BID [13]), which recently published data at 7 years of follow-up [14]. Overall, the data of the DURATION-1 to DURATION-6 studies showed a robust efficacy of ExQW, with mean HbA1c reductions of 1.3-1.9% and mean weight loss of 2-3.7 kg [8,15]. The safety profile was that expected from a GLP-1RA, with most frequent adverse events being of gastrointestinal (GI) nature: nausea, vomiting and diarrhea [8,16]. Particularly, there is a higher incidence of site-injection adverse events, most probably induced by a foreign body inflammatory reaction to injected microspheres [10]. However, the risk of GI side effects, especially nausea and vomiting, seems to be the lowest in the GLP-1RAs class [6,17]. Generally, long acting GLP-1RAs are associated with less nausea and vomiting but more diarrhea than shorter acting GLP-1RAs [17].

The latest two trials from this program published their results in the last year and led to important changes in the prescription practice. These are DURATION-7 (testing the association of ExQW to basal insulin) and DURATION-8 (testing the association of ExQW with the SGLT2i dapagliflozin).

ExQW studies published in 2017

DURATION 7 trial

The benefits of the association of exenatide BID to basal insulin on HbA1c and weight, as well as the durability of this effect have been already demonstrated [18]. Moreover, this association seems to be equally efficient in controlling blood glucose in comparison with basal bolus insulin treatment but is associated with decreased weight and lower risk of hypoglycemia [19]. DURATION-7 was the first

large scale randomized controlled trial to evaluate the efficacy and safety of the association of ExQW to basal insulin (insulin glargine) in T2DM patients not controlled by titrated insulin glargine (IG) and, eventually, metformin [20]. The study was multicentric, double blind and included 511 T2DM patients treated with IG±metformin. Patients initially entered an 8 week period of optimization of IG (forced titration of insulin dose). Patients with HbA1c between 7-10.5% after IG optimization were randomized 1:1 to receive ExQW (n=233) or placebo (n=231) on top of IG ±metformin. Randomized patients had a mean age of 57.7 years, a mean diabetes duration of 11.3 years and were mostly obese, with a mean BMI of 33.7 kg/m² [20]. They had rather poor metabolic control with a HbA1c of 8.5%, while the mean daily insulin glargine dose was 51 Units. After 28 weeks of randomized treatment, association of ExQW and insulin glargine decreased significantly HbA1c compared to placebo and insulin glargine, the mean difference being -0.7%. Overall, 32.5% of subjects treated with ExQW and IG reached the target HbA1c of <7%. In the same time, the mean weight difference between the two study groups was -1.5 kg in favor of the combination ExQW+IG [20]. When analyzing the evolution of individual cases over the 28 weeks of study treatment, the percentage of patients obtaining any degree of HbA1c decrease and weight loss was more than double for the combination ExQW+IG (51%) in comparison with patients treated with placebo+IG (23%) [21]. There were no unexpected safety findings during the study while incidence of hypoglycemic episodes was similar in the two treatment arms [20].

DURATION 8 trial

It was shown that both GLP-1RAs and SGLT-2i improve HbA1c and glycemic control

with the added benefit of weight loss and a low risk of hypoglycemia. DURATION-8 was the first large scale randomized controlled study to test the efficacy and safety of combining a GLP-1RA (ExQW) with a SGLT2i (dapagliflozin) [22]. This was a phase 3, multicentric, double-blind, randomized, active controlled, 28-week study with a 24-week (and subsequent 52-week) extension. The study included 695 T2DM subjects with poor metabolic control (baseline HbA_{1c} 8–12%, mean 9.3%) on metformin alone [22]. They were randomized 1:1:1 for treatment with ExQW + dapagliflozin, ExQW + placebo tablet and dapagliflozin + QW injected placebo. Over 28 weeks of treatment, combination of ExQW + dapagliflozin reduced HbA_{1c}, fasting (FPG) and postprandial (PPG) plasma glucose, weight and systolic blood pressure (SBP) significantly better than ExQW + placebo or dapagliflozin + placebo [22].

This year, during the EASD Annual Meeting in Lisbon, were presented the results of the first extension of 24 weeks of double blind therapy, making for a total of 52 weeks of follow-up [23]. From the total of 695 T2DM subjects originally randomized, 523 (75.3%) completed the 52 weeks on study treatment. At week 52, greater reductions of HbA_{1c} (1.75% vs. 1.38% vs. 1.23%) and body weight (3.3 kg vs. 1.5 kg vs. 2.3 kg) were recorded with the combination of ExQW + dapagliflozin compared to ExQW + placebo or dapagliflozin + placebo. The evolution of HbA_{1c}, weight and SBP was stable during the 24 week extension, with reductions recorded at week 52 being comparable with those recorded at week 28 [23].

Regarding safety, the combination of ExQW + dapagliflozin was well tolerated over 52 weeks, with comparable rates of adverse events in the three treatment arms. As expected, the most frequent AEs were GI and injection site nodules in ExQW treated patients and urinary

tract infections in dapagliflozin treated patients. No episodes of major hypoglycemia (loss of consciousness and blood glucose < 54 mg/dL requiring intervention of a third party for neurological recuperation) were recorded during 52 weeks of treatment. No deaths were recorded in the 28 to 52 weeks extension [23].

Overall, the 1-year data of the DURATION-8 trial [23] indicate the efficacy and safety of the ExQW + dapagliflozin combination, with a durable effect on HbA1c, weight and SBP and an expected safety profile.

EXSCEL Trial

In 2008, the FDA gave new guidelines for the pharma industry, imposing practically that all new medications from the modern anti-diabetes drug classes (including those recently approved on market) have to be tested for cardiovascular (CV) safety in a dedicated large scale CV outcome trial [24]. For ExQW, this study was named EXSCEL (EXenatide Study of Cardiovascular Event Lowering) and was initiated in June 2010 [25]. The study was academically coordinated by the Oxford Diabetes Trial Unit in the UK and Duke Clinical Research Institute in the USA. The primary aim of EXSCEL was to assess the effect of ExQW (compared to placebo) on major adverse cardiovascular events (MACE) when added to standard of care in T2DM patients with high CV risk [25,26]. According to the FDA recommendations, the primary outcome was the time to first occurrence of any component of a classical three-composite MACE – CV death, nonfatal myocardial infarction (MI) or nonfatal stroke.

Finally the study included a total of 14752 subjects, with a mean age of 62.7 years, mean diabetes duration of 12 years and “medium” diabetes control with a HbA1c of 8.0%. At baseline a total of 76.5% of patients were treated

with metformin and 46.2% with insulin. Patients received also standard treatment for CVD, including antiplatelet treatment (69.9% of patients), statin (73.5% of patients) and anti-hypertensive treatment (90.3% of patients). Overall 73% of patients had at least one previous CV event and 27% had multiple CV risk factors [25,26].

After a median follow-up of 3.2 years, the EXSCEL study published its results in September 2017 [26], results that were concomitantly presented during the EASD Annual Meeting in Lisbon. Finally, patients treated with ExQW had a non-significant ($p=0.06$) 9% decrease of the risk for the primary outcome, with a Hazard Ratio (HR) of 0.91 (95%CI 0.83-to-1.00) [26]. However, the study met one of its main objectives and proved ($p<0.001$ for non-inferiority versus placebo) the CV safety of ExQW treatment. Interestingly, patients treated with ExQW had 14% lower risk for all cause mortality and 12% lower risk for CV mortality but these differences were considered not statistically significant due to failure of proving superiority for the primary outcome. There were no safety issues associated with the long use of ExQW in EXCEL, including hospitalizations for heart failure, acute pancreatitis or pancreatic cancer and thyroid C-cell carcinoma [26].

A profound discussion of the results of EXSCEL in the context of those of similar studies with other long acting GLP-1RAs (such as liraglutide – LEADER and semaglutide – SUSTAIN6) is beyond the scope of this editorial. However, we should mention as possible explanations for the “disappointing” lack of CV protection the rather short duration of the trial, low baseline HbA1c, increased rate of discontinuation of study drug and increased use in the placebo group of drugs with already

proven CV benefits like SGLT2i and other GLP-1RAs [26].

New perspectives for ExQW

As a consequence of the publication of DURATION-7 and DURATION-8 trials, the Committee for Medicinal Products for Human Use of the EMA has approved an update to the summary of product characteristics (SmPC) for ExQW [27], authorizing the use of ExQW in combination with basal insulin, respectively with an SGLT2i for those patients failing to reach glycemic targets on maximally tolerated doses of the other diabetes therapies. These changes were also adopted in the SmPC in Romania, being effective as of November 2017.

Recently, the ExQW injection was made easier following the development of a once weekly suspension for autoinjection [28]. For this, the polymer microspheres were diluted in a solution of triglycerides (Miglyol 812) in a simplified autoinjector pen. This easy to use single dose auto-injector device

(Bydureon®BCise™) was recently approved by the FDA in the USA [29] and will be available starting with 2018.

For the while, with the announced withdrawal of albiglutide (and until other new molecules will be approved), ExQW will remain, together with dulaglutide, the only available GLP-1RAs with weekly administration.

Duality of interest: Cristian Guja served as the international coordinating investigator in DURATION-7 and was a trial investigator in DURATION-8 studies, both sponsored by Astra Zeneca. He also participated in scientific advisory boards and received consulting fees from Alfa Wasserman, AstraZeneca, Bayer AG, Boehringer Ingelheim, Berlin-Chemie Mennarini, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, and Sanofi.

Doina Andrada Mihai participated in scientific advisory boards and received consulting fees from Eli Lilly, Novo Nordisk, Sanofi, and Servier.

REFERENCES

1. **International Diabetes Federation.** IDF Diabetes Atlas – 8th Edition. Accessed at: <http://www.diabetesatlas.org/> on 2 Dec 2017
2. **Burrows NR, Hora I, Geiss LS, Gregg EW, Albright A.** Incidence of end-stage renal disease attributed to diabetes among persons with diagnosed diabetes - United States and Puerto Rico, 2000-2014. *Morb Mortal Wkly Rep* 66: 1165-1170, 2017.
3. **Montvida O, Shaw J, Atherton JJ, Stringer F, Paul SK.** Long-term trends in antidiabetes drug usage in the U.S.: Real-world evidence in patients newly diagnosed with type 2 diabetes. *Diabetes Care* Nov 6. pii: dc171414. doi: 10.2337/dc17-1414, 2017. [Epub ahead of print]
4. **American Diabetes Association.** Pharmacologic approaches to glycemic treatment, Sec. 8 in Standards of Medical Care in Diabetes—2017. *Diabetes Care* 40[Suppl. 1]: S64–S74, 2017.
5. **Edelman SV, Polonsky WH.** Type 2 diabetes in the real world: the elusive nature of glycemic control. *Diabetes Care* 40: 1425-1432, 2017.
6. **Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, Khunti K, Davies MJ.** Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis. *Diabetes Obes Metab* 19: 524-536, 2017.
7. **Malone J, Trautmann M, Wilhelm K, Taylor K, Kendall DM.** Exenatide once weekly for the treatment of type 2 diabetes. *Expert Opin Investig Drugs* 18:359-367, 2009.
8. **Knop FK, Brønden A, Vilsbøll T.** Exenatide: pharmacokinetics, clinical use, and future directions. *Expert Opin Pharmacother* 18: 555-571, 2017.
9. **Abd El Aziz MS, Kahle M, Meier JJ, Nauck MA.** A meta-analysis comparing clinical effects of short- or long-acting GLP-1 receptor agonists versus insulin

treatment from head-to-head studies in type 2 diabetic patients. *Diabetes Obes Metab* 19: 216-227, 2017.

10. DeYoung MB, MacConell L, Sarin V, Trautmann M, Herbert P. Encapsulation of exenatide in poly-(D,L-lactide-co-glycolide) microspheres produced an investigational long-acting once-weekly formulation for type 2 diabetes. *Diabetes Technol Ther* 13: 1145-1154, 2011.

11. Fineman M, Flanagan S, Taylor K et al. Pharmacokinetics and pharmacodynamics of exenatide extended-release after single and multiple dosing. *Clin Pharmacokinet* 50: 65-74, 2011.

12. LaRue S, Malloy J. Evaluation of the dual-chamber pen design for the injection of exenatide once weekly for the treatment of type 2 diabetes. *J Diabetes Sci Technol* 9: 815-821, 2015.

13. Buse JB, Drucker DJ, Taylor KL et al. DURATION-1: exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. *Diabetes Care* 33: 1255-1261, 2010.

14. Wysham CH, Philis-Tsimikas A, Klein EJ et al. DURATION-1 extension in patients with T2D: efficacy and tolerability of exenatide once weekly (QW) over 7 years. *Diabetes* 65[Suppl. 1]: A271, 2016. (Abstract 1041-P) - Presented at ADA 76th Scientific Sessions; New Orleans, USA, 10-14 Jun 2016.

15. Kayaniyl S, Lozano-Ortega G, Bennett HA et al. A network meta-analysis comparing exenatide once weekly with other GLP-1 receptor agonists for the treatment of type 2 diabetes mellitus. *Diabetes Ther* 7: 27-43, 2016.

16. MacConell L, Gurney K, Malloy J et al. Safety and tolerability of exenatide once weekly in patients with type 2 diabetes: an integrated analysis of 4,328 patients. *Diabetes Metab Syndr Obes* 8: 241-253, 2015.

17. Bettge K, Kahle M, Abd El Aziz MS, Meier JJ, Nauck MA. Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: A systematic analysis of published clinical trials. *Diabetes Obes Metab* 19: 336-347, 2017.

18. Buse JB, Bergenstal RM, Glass LC et al. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. *Ann Intern Med* 154: 103-112, 2011.

19. Diamant M, Nauck MA, Shaginian R et al. Glucagon-like peptide 1 receptor agonist or bolus insulin

with optimized basal insulin in type 2 diabetes. *Diabetes Care* 37: 2763-2773, 2014.

20. Frias JP, Rosenstock J, Somogyi A et al. Efficacy and safety of exenatide qw vs. placebo added to insulin glargine in uncontrolled basal-insulin treated type 2 diabetes: DURATION-7 trial. *Diabetes* 60[Suppl 1]: A34, 2017. (Abstract 132-OR) – Presented at ADA 77th Scientific Sessions, San Diego, USA, 9-13 June 2017.

21. Hardy E, Rosenstock J, Frias JP et al. Individual HbA1c and weight responses to exenatide QW or placebo added to titrated insulin glargine in type 2 diabetes uncontrolled after insulin optimisation in the DURATION-7 study. *Diabetologia* 66[Suppl 1]: S3, 2017. (Abstract 3) – Presented at EASD Annual Meeting, Lisbon, Portugal, 12-15 September 2017.

22. Frías JP, Guja C, Hardy E et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol* 4: 1004-1016, 2016.

23. Guja C, Frias JP, Ahmed AA et al. DURATION-8 randomised controlled trial 1-year results: efficacy and safety of once-weekly exenatide plus once-daily dapagliflozin versus exenatide or dapagliflozin alone. *Diabetologia* 60[Suppl 1]: S5, 2017. (Abstract 6) - 53rd EASD Annual Meeting, Lisbon, Portugal, 12-15 September 2017.

24. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for industry; Diabetes mellitus - evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes, 2008. Accessed on 2 Dec 2017 at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf>

25. Mentz RJ, Bethel MA, Gustavson S et al. Baseline characteristics of patients enrolled in the exenatide study of cardiovascular event lowering (EXSCEL). *Am Heart J* 187: 1-9, 2017.

26. Holman RR, Bethel MA, Mentz RJ et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 377: 1228-1239, 2017.

27. European Medicines Agency. Summary of opinion (post authorization). Accessed at:

http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/002020/WC500231692.pdf on 02 Dec 2017.

28. Gadde KM, Vetter ML, Iqbal N et al. Efficacy and safety of autoinjected exenatide once-weekly suspension versus sitagliptin or placebo with metformin in patients with type 2 diabetes: The DURATION-NEO-2 randomized clinical study. *Diabetes Obes Metab* 19: 979-988, 2017.

29. *** US FDA approves new easy-to-use, once-weekly BYDUREON[®]BCise[™] injectable medicine for patients with type-2 diabetes. Accessed at: <https://www.astrazeneca-us.com/media/press-releases/2017/us-fda-approves-new-easy-to-use-once-weekly-bydureon-bcise-injectable-medicine-for-patients-with-type-2-diabetes-10232017.html> on 02 Dec 2017.