Accepted Manuscript

Title: Real-world clinical experience of Xultophy in the management of patients with type 2 diabetes in a secondary care clinic

Authors: David M. Williams, Natasha Shrikrishnapalasuriyar, Waheeba Syed, Win L. Yin, Richard Chudleigh, Stephen C. Bain, David E. Price, Jeffrey W. Stephens

PII: S1871-4021(18)30259-5
DOI: https://doi.org/10.1016/j.dsx.2018.06.029
Reference: DSX 1039

To appear in: *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*

Please cite this article as: Williams DM, Shrikrishnapalasuriyar N, Syed W, Yin WL, Chudleigh R, Bain SC, Price DE, Stephens JW, Real-world clinical experience of Xultophy in the management of patients with type 2 diabetes in a secondary care clinic, *Diabetes and Metabolic Syndrome: Clinical Research and Reviews* (2018), https://doi.org/10.1016/j.dsx.2018.06.029

Real-world clinical experience of Xultophy in the management of patients with type 2 diabetes in a secondary care clinic

David M Williams MRCP[1,2*], Natasha Shrikrishnapalasuriyar MRCP[1*], Waheeba Syed MRCP[1], Win L Yin MRCP[1], Richard Chudleigh MBBCh, MD FRCP[3], Stephen C Bain MA, MD, FRCP[2,3], David E Price MA, MD, FRCP[1], Jeffrey W Stephens BSc, MBBS, PhD, FRCP[1,2]

1. Department of Diabetes & Endocrinology, Morriston Hospital, Swansea, SA6 6NL
2. Diabetes Research Group, School of Medicine, Swansea University, Swansea SA2 8PP
3. Department of Diabetes & Endocrinology, Singleton Hospital, Swansea SA2 8QA.

* These authors contributed equally

Correspondence to:

Dr David M Williams

Diabetes Centre

Morriston Hospital

Swansea

SA6 6NL

Email: david.williams@doctors.org.uk

Tel: +44(0)1792704078

Abstract

Aims

Xultophy is the first fixed co-formulation pen containing insulin degludec and the glucagon-like peptide-1 (GLP-1) analogue liraglutide, authorized for type 2 diabetes patients since 2014. The aim was to review the clinical effectiveness of Xultophy across two hospitals in Wales.

Methods

Retrospective review of patients commenced on Xultophy between April 2016 and January 2018 was taken. Data related to glycemic control, weight and medication use were collected.

Results

Ninety-one patients were initiated on Xultophy, and 60 patients had follow-up for at least 6 months with a mean age of 57.3 years (47% male). Xultophy was well-tolerated, however, abdominal cramps and nausea limited use in three patients. Baseline HbA1c and weight were 84.7mmol/mol and 101.5kg. There were significant HbA1c reductions of 9.9mmol/mol ($p<0.0001$) and 13.4mmol/mol ($p<0.008$) at 6 and 12 months, and non-significant changes in weight. Patients with an HbA1c over 84mmol/mol showed the greatest HbA1c improvement over 6-months. Those prescribed insulin prior to Xultophy had less significant improvements in HbA1c than those previously prescribed GLP-1 analogues.

Conclusions

There were significant reductions in HbA1c and statistically insignificant weight gain over 12 months. Switching from GLP-1 analogues to Xultophy was associated with a greater HbA1c reduction compared to switching from insulin.

Keywords: Xultophy, glucagon-like peptide 1 analogues, liraglutide, insulin, degludec

Introduction

Type 2 diabetes (T2D) is a progressive multi-system disorder, characterized by impaired post-prandial insulin secretion, increased peripheral insulin resistance and abnormal post-prandial incretin release. At the time of diagnosis, most people with T2D have lost between 50-80% of their β-cell function (1). The targeted manipulation of several key biological pathways responsible for disease progression is important, and is increasingly exploited with our improving understanding of the underlying pathophysiology of diabetes and ever-growing number of pharmacological options used to treat the disease (1). As a result, patients with T2D are sequentially initiated on several oral hypoglycemic agents with the addition of basal insulin when oral agents fail to achieve the patient's glycemic target. The titration of basal insulin is recommended for the targeted control of fasting plasma glucose (FPG) (2), but fails to significantly address the postprandial glucose (PPG) excursions which typically characterize the earlier stages of deteriorating glycemic control (3). Indeed, over 70% of patients with T2D fail to achieve an HbA1c target of 7.0% (53mmol/mol) using basal insulin and thus require treatment intensification (4).

Traditionally, patients with T2D who are unable to adequately maintain glycemic control using basal insulin would require the addition of prandial insulin or a switch to pre-mixed insulin formulations (2). The addition of prandial insulin aims to address the worsening PPG levels which are associated with worse cardiovascular outcomes and all-cause mortality (5), and are frequently seen as the first sign of progressive β-cell failure (3). However, treatment intensification with prandial insulin is associated with

greater weight gain, hypoglycaemia and difficulties with treatment adherence such as insulin dose calculations, which often impede appropriate insulin intensification.

As a result, targeting PPG excursions with alternative agents is an attractive management option. One class of drugs being increasingly used for this purpose are the glucagon-like peptide-1 (GLP-1) analogues, which have been available since the introduction of exenatide in 2005 (not in the UK until 2007). Since then several other GLP-1 analogues have been approved for use, including dulaglutide (2014), liraglutide (2009) and lixisenatide (2013) (6). The use of these medications significantly improves glycemic control, with one recent meta-analysis demonstrating an HbA1c improvement of 0.9-1.4% (10-15 mmol/mol) over 6 months, with the authors concluding that 50% of patients using GLP-1 analogues will achieve HbA1c <7.0% within 6 months (7). Their effect on HbA1c are due to their targeting of PPG levels whilst improving weight loss and reducing hypoglycemia risk compared with insulin (2). Whilst these trial data are very encouraging, real-world data indicate that this benefit may not be as good in practice. Hall and colleagues found that T2D patients using a GLP-1 analogue improved their HbA1c by just 0.6% over 12 months (8), highlighting the difference between trial and real-world data. This is likely a result of the increased treatment adherence that is noted by participants in clinical trials compared with patients in the 'real-world'. This has been noted previously in studies investigating the benefits of GLP-1 analogues in T2D patients to account for about 75% of this difference (9).

The mechanism underlying the improved glycemic control associated with basal insulin and GLP-1 analogues are likely to complement each other, targeting both the FPG and PPG. As a result, combination therapies of GLP-1 analogues and basal insulin have been developed and approved for clinical use. Xultophy is a combination of basal

insulin degludec and the GLP-1 analogue liraglutide, introduced by Novo Nordisk, and approved for use in 2014 (6). NICE recommend the initiation of GLP-1 analogues in T2D patients who have poor glycemic control despite triple therapy, and a body mass index greater than 35kg/m^2, in a specialist care setting, though there is less specific guidance on combination therapies such as Xultophy (10). Meta-analysis of randomized-controlled trials evaluating Xultophy found that it is effective, with HbA1c reductions of 1.89% (21 mmol/mol) and a non-significant weight loss of about 0.81kg (11). However, there are few real-world data published on the efficacy of this combination regime. In this paper, we evaluate the real-world efficacy of Xultophy in T2D patients across two hospital sites in Swansea.

Methods

Subjects

A total of 91 T2D patients were identified from our local electronic database who had been commenced on Xultophy between April 2016 and January 2018. These patients attended follow-up in secondary care across two hospitals; Morriston and Singleton hospitals in Swansea. The original analysis of the data took place in March 2018.

We aimed to review the variables at the follow-up visit after 6 months and 12 months of starting Xultophy, however, patients were not commenced on Xultophy at the same time so therefore at the time of analysis follow-up data was not available for all subjects. Outcomes which were reviewed at follow-up included HbA1c, weight, Body Mass Index (BMI), Blood Pressure (BP) and estimated Glomerular Filtration Rate (eGFR). Data were also collected on previous glucose-lowering therapies that the patients had been using prior to commencing Xultophy, including oral agents and insulin.

Statistical Analysis

Paired t tests were used to compare HbA1c, weight, BMI and BP at follow-up at 6 and 12 months. The mean and standard deviation were used to describe these variables. A Wilcoxon signed ranks test was used for the outcome eGFR which were shown by the median and interquartile range.

Results

Baseline characteristics of patients

At baseline, the sample had mean age 57.3 ±10.3 years, HbA1c 84.7 ±15.2 mmol/mol (9.9 ±1.3%), weight 101.5 ±20.5 kg and BMI of 35.6 ±6.8 kg/m^2. Of the 91 patients commenced on Xultophy, 60 had follow-up data following the first visit. In this cohort, 47% of the patients were male. Prior to Xultophy initiation, 24 patients were prescribed a GLP-1 analogue, 26 prescribed basal insulin and 16 on both basal insulin and GLP-1 analogue. Four patients were prescribed a combination of metformin, sulphonylurea and insulin, 2 patients were prescribed metformin, sulphonylurea and a sodium-glucose co-transporter-2 (SGLT-2) inhibitor, 2 prescribed a combination of metformin, SGLT-2 inhibitor, insulin and GLP-1 analogue, 1 patient was prescribed metformin, dipeptidyl peptidase-4 inhibitor (DPP-IVi) and insulin, and 1 patient was prescribed SGLT-2 inhibitors, GLP-1 analogue and insulin. Three patients were not prescribed any pharmacotherapy prior to commencing Xultophy. The drug therapy used in these patients prior to the initiation of Xultophy is summarized in Figure 1. Of the 91 patients commenced on treatment with Xultophy, 3 discontinued treatment, 2 due to abdominal cramps and 1 due to nausea.

Changes in glycemic control observed with therapy

Significant improvements in glycemic control were observed during follow-up. In the 60 patients with 6-month follow-up data available, the mean HbA1c improved from 84.7 ±15.2 mmol/mol (9.9 ±1.3%) at baseline to 74.8 ±16.1 mmol/mol (9.0 ±1.4%) (-9.9 mmol/mol (0.9%), P< 0.0001). In the 25 patients with 12-month follow up data, a statistically significant improvement in the HbA1c was noted from a baseline 84.5 ±13.2 mmol/mol (9.9 ±1.1%) to 71.1 ±16.7 mmol/mol (8.7 ±1.4%) (-13.4 mmol/mol (1.2%), P=0.008). We observed statistically non-significant changes in body weight from 101.5 ±20.5 kg at baseline to 102.4 ±20.5 kg at 6 months (P=0.26) and from 95.3 ±19.2 kg to 96.3 ±21.2 kg (P=0.54) in those with 12-month follow-up data. Table 1 and Table 2 summarize these data at 6 and 12-months, respectively.

We chose a priori to divide into two groups by the median HbA1c (84 mmol/mol (9.8%)) to look at response status by HbA1c at 6 months. There was a greater reduction observed in the HbA1c in patients with a baseline HbA1c greater than 84 mmol/mol (9.8%) (Pre-treatment v post-treatment: 97.6 ±7.0 v 80.7 ±17.6, P<0.0001) compared with patients with an HbA1c less than 84 mmol/mol (9.8%) (Pre-treatment v post-treatment: 73.3 ±8.3 v 69.5 ±12.9, P=0.07).

Patients prescribed insulin ± oral hypoglycemic agents prior to the initiation of Xultophy had a statistically non-significant improvement in the HbA1c of -4.0 mmol/mol (0.4%) (P=0.39), and a non-significant weight gain of 1.3 kg (P=0.84) over 6 months. Conversely, patients prescribed a GLP-1 analogue ± oral hypoglycemic

agents prior to Xultophy were noted to have a significant improvement in HbA1c of -13.7 mmol/mol (1.3%) (P=0.01) and a non-significant weight gain of 1.7 kg (P=0.13). Patients prescribed both insulin and a GLP-1 analogue ± oral hypoglycemic agents, before the initiation of Xultophy were observed to improve their HbA1c by 11.7 mmol/mol (1.1%) over 6 months (P=0.02) and have a non-significant weight gain of 1.9 kg (P=0.23). The data related to patients using insulin, GLP-1 analogues or both insulin and GLP-1 analogues ± oral hypoglycemic agents are presented in Table 3.

For those patients taking insulin only who were switched to Xultophy, we observed no statistically significant change in insulin dose before and after the change to Xultophy, calculated from the dose steps of Xultophy. The total daily insulin dose pre- and post-Xultophy were 39 [interquartile range: 24-75] and 39 [24-46], P=0.25.

Additionally there were some changes in BP and eGFR at 6 and 12 months. There were statistically non-significant changes in the systolic BP, diastolic BP and at 6 months compared with baseline. At 12 months, further changes in these parameter were noted in the systolic BP (132 vs 133, P=0.59), diastolic BP (78 vs 82, P=0.03) and eGFR (89.0 vs 90.0, P=0.17) compared with baseline. Table 1 and Table 2 summarize these data at 6 and 12-months, respectively.

Discussion

The management of diabetes has evolved over the last 20 years to include greater focus on the management of cardiovascular risk as well as glycemic control. Xultophy is the first fixed co-formulation pen containing basal insulin (degludec) and a GLP-1 analogue (liraglutide), approved for use in patients with T2D since 2014. Few ‘real-

world' data are available in respect of Xultophy use, because many centers have only recently started to use Xultophy in clinical practice.

In this analysis, patients who were initiated on Xultophy demonstrated a statistically significant improvement in the HbA1c after 6 and 12 months of using the combination drug. The improvement was most notable in patients whose baseline HbA1c was greater than 84 mmol/mol (9.8%). This could be because patients who were initially prescribed a more than once a day insulin were struggling to manage their diabetes and fully comply with treatment with missed doses, finding it easier to manage with the once daily injection used with Xultophy.

A meta-analysis conducted by Orme and colleagues (7) found that GLP-1 analogues significantly improved both weight loss and overall glycemic control. One randomized trial found a non-inferior significant HbA1c reduction in patients with poorly-controlled T2D using the combination degludec and liraglutide compared with continued uptitration of basal insulin glargine. The study also observed a weight loss of 1.4 kg over 6 months in those using combination degludec/liraglutide compared with 1.8kg weight gain in those using insulin glargine alone (12). Furthermore, one systematic review demonstrated that Xultophy use resulted in a significant HbA1c reduction of 1.3-1.9% (14-21 mmol/mol) in patients with T2D who were previously using oral hypoglycemic agents, GLP-1 analogues or basal insulin (13).

The results presented in this paper demonstrate that Xultophy was a weight-neutral combination therapy at 6 or 12 months. This may be because of varied compliance with dietary and lifestyle measures which support weight loss. Alternatively, it may be that

the weight-gain effect of insulin is overcome with the combination of the GLP-1 analogue, meaning patients gain the benefit in glycemic control associated with insulin, without the associated weight gain. Indeed, a meta-analysis conducted by Cai and colleagues (11) did not show any significant overall weight reduction with Xultophy in randomized-controlled trials, though it confirmed the significant improvement in HbA1c associated with its use.

We also observed that patients who were prescribed insulin ± oral agents at the time of Xultophy initiation had a lesser improvement in HbA1c compared to those who are either on GLP-1 analogues or both insulin and GLP-1 analogues ± oral agents. This may imply that these patients had a longer duration of diabetes and therefore less remaining beta-cell function.

In conclusion, Xultophy is an effective drug in the intensification of glycemic control in patients with T2D who are inadequately controlled using oral antidiabetic medications, GLP-1 analogues and to a lesser extent, basal insulin alone.

Limitations

Xultophy has only been recently recognized as a new therapy for patients with T2D and therefore, limited follow-up was available for these patients. Longer term follow-up may demonstrate further changes in HbA1c and/or weight, which would further add to these findings.

Conflict of interest statement

The authors of this manuscript certify that they have no affiliation or involvement with any organization with any financial or non-financial interest in the subject matter which is described in this manuscript.

References

1. DeFronzo RA, Eldor R, Abdul-Ghani M. Pathophysiologic approach to therapy in patients with newly diagnosed type 2 diabetes. Diabetes care. 2013;36(Supplement 2):S127-S38.
2. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes care. 2015;38(1):140-9.
3. Monnier L, Colette C, Dunseath GJ, Owens DR. The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. Diabetes care. 2007;30(2):263-9.
4. Dale J, Martin S, Gadsby R. Insulin initiation in primary care for patients with type 2 diabetes: 3-year follow-up study. Primary care diabetes. 2010;4(2):85-9.
5. Cavalot F, Pagliarino A, Valle M, Di Martino L, Bonomo K, Massucco P, et al. Postprandial blood glucose predicts cardiovascular events and all-cause mortality in type 2 diabetes in a 14-year follow-up: lessons from the San Luigi Gonzaga Diabetes Study. Diabetes care. 2011;34(10):2237-43.
6. Kang YM, Jung CH. Cardiovascular effects of glucagon-like peptide-1 receptor agonists. Endocrinology and Metabolism. 2016;31(2):258-74.
7. Orme ME, Nguyen H, Lu JY, Thomas SA. Comparative effectiveness of glycemic control in patients with type 2 diabetes treated with GLP-1 receptor agonists: a network meta-analysis of placebo-controlled and active-comparator trials. Diabetes, metabolic syndrome and obesity: targets and therapy. 2017;10:111.

8. Hall G, McMahon A, Dain MP, Wang E, Home P. Primary‐care observational database study of the efficacy of GLP‐1 receptor agonists and insulin in the UK. Diabetic Medicine. 2013;30(6):681-6.
9. Carls GS, Tuttle E, Tan R-D, Huynh J, Yee J, Edelman SV, et al. Understanding the gap between efficacy in randomized controlled trials and effectiveness in real-world use of GLP-1 RA and DPP-4 therapies in patients with type 2 diabetes. Diabetes care. 2017;40(11):1469-78.
10. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. NICE guideline [NG28]. 2017 [Available from: https://www.nice.org.uk/guidance/ng28/chapter/1-recommendations
11. Cai X, Gao X, Yang W, Ji L. Comparison between insulin degludec/liraglutide treatment and insulin glargine/lixisenatide treatment in type 2 diabetes: a systematic review and meta-analysis. Expert opinion on pharmacotherapy. 2017;18(17):1789-98.
12. Lingvay I, Manghi FP, García-Hernández P, Norwood P, Lehmann L, Tarp-Johansen MJ, et al. Effect of insulin glargine up-titration vs insulin degludec/liraglutide on glycated hemoglobin levels in patients with uncontrolled type 2 diabetes: the DUAL V randomized clinical trial. Jama. 2016;315(9):898-907.
13. Harris K, Nealy KL. The Clinical Use of a Fixed-Dose Combination of Insulin Degludec and Liraglutide (Xultophy 100/3.6) for the Treatment of Type 2 Diabetes. Annals of Pharmacotherapy. 2018;52(1):69-77.

Figure 1 Diabetes therapies used by patients in our cohort prior to the initiation of Xultophy.

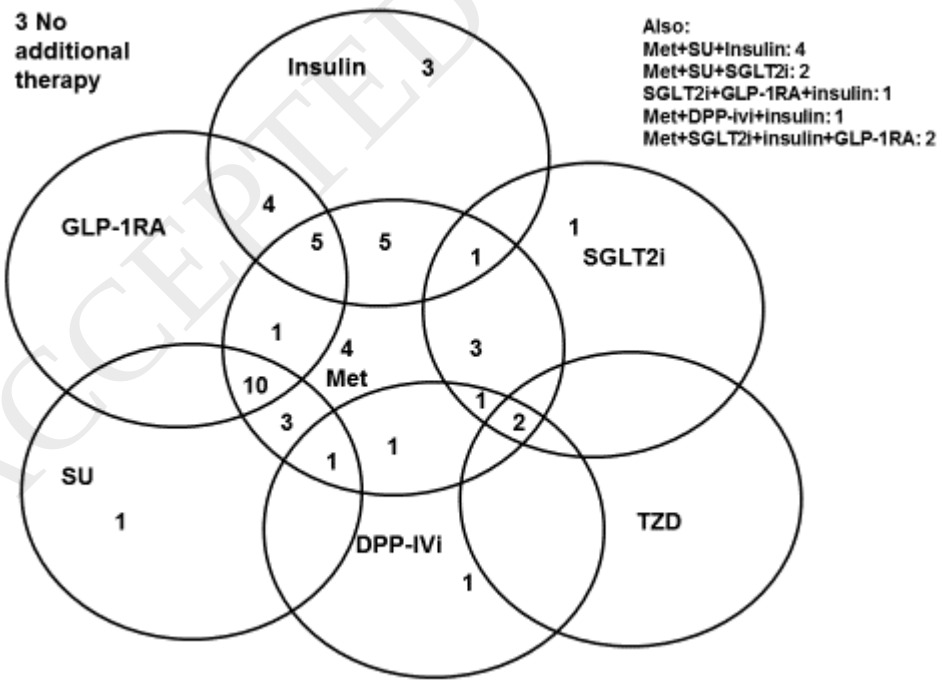

Table 1: Glycaemic and weight changes at six months

Variable	Baseline (n=60)	6 months (n=60)	P value
HbA1c (mmol/mol)	84.7 (15.2)	74.8 (16.1)	<0.0001
Weight (kg)	101.5 (20.5)	102.4 (20.5)	0.26
Systolic blood pressure (mmHg)	136 (16)	136 (15)	0.87
Diastolic blood pressure (mmHg)	79 (7)	81 (7.3)	0.05
Estimated GFR*	89.0 [70.3-90.0]	85.0 [73.0-90.0]	0.18

Table 1: Changes in HbA1c and body weight from baseline to six months. *Wilcoxon signed Ranks test. Median and Interquartile range shown. Mean (SD) presented for other data and statistical significance was determined by paired t test.

Table 2: Glycaemic and weight changes at twelve months

Variable	Baseline (n=60)	6 months (n=60)	P value
HbA1c (mmol/mol)	84.5 (13.2)	71.1 (16.7)	0.008
Weight (kg)	95.3 (19.2)	96.3 (21.2)	0.54
Systolic blood pressure (mmHg)	132 (15)	133 (15)	0.59
Diastolic blood pressure (mmHg)	78 (6)	82 (6)	0.03
Estimated GFR*	89.0 [70.3-90.0]	90.0 [72.0-90.0]	0.17

Table 2: Changes in HbA1c and body weight from baseline to twelve months. *Wilcoxon signed Ranks test. Median and Interquartile range shown. Mean (SD) presented for other data and statistical significance was determined by paired t test.

Table 3: The impact of previous injectable therapy on response to Xultophy

Variable	Baseline	6 months	P value
Patients previously using insulin (n=13)			

HbA1c	89.3 (21.9)	85.3 (18.8)	0.39
Weight	100.5 (16.6)	101.8 (19.6)	0.84
Patients previously using GLP-1 analogues (n=11)			
HbA1c	86.0 (10.9)	72.3 (15.9)	0.01
Weight	111.2 (24.3)	112.9 (24.3)	0.13
Patients previously using GLP-1 analogues and insulin (n=12)			
HbA1c	79.9(11.6)	68.2 (13.6)	0.02
Weight	91.4 (20.8)	93.3 (20.5)	0.23

Table 3: Differences in glycaemic and weight changes in response to the initiation of Xultophy over 6 months between patients previously using insulin, GLP-1 analogues or both. Data are presented as the mean (SD) and statistical significance was determined by paired t test.