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Review

Efficacy and adherence of glucagon-like peptide-1 receptor agonist treatment in patients with type 2 diabetes mellitus in real-life settings

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ABSTRACT

Despite the availability of a large number of therapeutic options throughout the world, rates of optimal glycaemic control in adult patients with type 2 diabetes mellitus remain low. Delays in treatment intensification to insulin and low adherence to insulin regimes, which are well-documented contributors to poor glycaemic control, are in many cases driven by fear of hypoglycaemic events, weight gain and injections. Over the last 10 years, injectable glucagon-like peptide-1 receptor agonists (GLP1-RAs) have emerged as alternatives to basal insulin for treatment intensification in patients inadequately controlled with oral antidiabetic drugs. As a class, GLP1-RAs are associated with weight loss and fewer hypoglycaemic events than insulin. In addition, some of them are available in once-a-week formulations and therefore require fewer injections. However, as randomized controlled trials are not representative of everyday practice, physicians should consider the results of real-life studies to guide their treatment decisions. In this review, while significant variations in efficacy, tolerability and adherence data were noted from one study to another, rates of glycaemic control overall were low. Indeed, our present analysis has suggested that regular re-evaluations of treatment, including response, tolerability, adherence, cost and quality of life, are necessary.

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic progressive disease that typically requires pharmacological intervention for patients to achieve and maintain long-term glycaemic control. Yet, despite the availability of a large number of therapeutic options throughout the world, rates of optimal glycaemic control – recommended as < 7% for the majority of T2DM patients, but depending on age and/or comorbidities – are low. In the US, the National Health and Nutrition Examination Survey (NHANES) up to 2010 found that the rate of control plateaued at 50–60% of patients [1]. The reasons for poor glycaemic control are complex, and include issues such as low treatment adherence and persistence over time, as well as disease progression and delays in treatment intensification [2]. A 2012 study showed that 64% of general practitioners considered that patient resistance to treatment intensification was a barrier to insulin initiation and that 80% of them felt that the potential for non-adherence discouraged them from initiating insulin [3]. Fear of injections, hypoglycaemia and weight gain have also been reported as reasons for non-adherence. In the French arm of the second Diabetes Attitudes, Wishes and Needs (DAWN2) study, > 70% of physicians reported in 2012 that it would be helpful to have diabetes medications that were associated with a lower risk of hypoglycaemia [4].

Over the last 10 years, glucagon-like peptide-1 receptor agonists (GLP1-RAs) have emerged as alternatives to basal insulin. These are incretin mimetics that reproduce the effects of endogenous glucagon-like peptide-1 and, as such, stimulate glucose-dependent pancreatic insulin secretion and suppress pancreatic glucagon. They also reduce postprandial glycaemia and induce satiety by slowing gastric-emptying. European and

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Abbreviations

AWARD-2 assessment of weekly administration of dulaglutide in diabetes-2
BID twice a day
CHOICE changes to treatment and outcomes in patients with type 2 diabetes initiating injectable therapy
CI confidence interval
DAWN2 diabetes attitudes, wishes and needs (second study)
DURATION diabetes therapy utilization: researching changes in A1C, weight and other factors through intervention with exenatide once weekly
eGFR estimated glomerular filtration rate
EVIDENCE observational study on efficacy and safety of liraglutide in subjects with type 2 diabetes
GLP1-RA glucagon-like peptide-1 receptor agonist
HbA_{1c} haemoglobin A_{1c}
LEADER liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results
MPR medication possession ratio
NHANES national health and nutrition examination survey
NICE national institute for health and clinical excellence
PDC proportion of days covered
QALY quality-adjusted life-year
QD once a day
QW once a week
RCT randomized controlled trial
THIN The health improvement network
UK United Kingdom
US United States

American guidelines for glycaemic control in patients with T2DM list GLP1-RAs as alternatives to insulin for treatment intensification in patients inadequately controlled with oral antidiabetic drugs (OADs) [5].

Currently, nine formulations of injectable GLP1-RAs have been approved for the treatment of T2DM by the European Medicines Agency and/or the US Food and Drug Administration: exenatide twice a day (BID; European/US approval: 2006/2005); liraglutide once a day (QD; European/US approval: 2009/2010); exenatide once a week (QW; European/US approval: 2011/2012); albiglutide QW (European/US approval: 2014); dulaglutide QW prefilled pen (European/US approval: 2014); exenatide QW pen (US approval: 2014); lixisenatide QD (European/US approval: 2013/2016); exenatide QW single-dose auto-injector device (US approval: 2017); and semaglutide QW (European/US approval: 2017/2017).

Randomized controlled trials (RCTs) have shown that treatment with GLP1-RAs reduces haemoglobin A_{1c} (HbA_{1c}) and weight, improves cardiovascular risk factors and rarely induces hypoglycaemic events [6,7,8]. Improvement in cardiovascular outcomes compared with placebo has also been shown in liraglutide QD, semaglutide and albiglutide QW RCTs [9,10,11]. The most frequent class-specific adverse events are gastrointestinal symptoms, such as nausea and vomiting.

These promising RCT results suggest that, with GLP1-RAs, there should be fewer barriers to treatment intensification, particularly because of the absence of drug titration and blood glucose monitoring. Adherence and persistence are likely to improve due to less cumbersome schedules, fewer hypoglycaemic side-effects and greater weight loss, such that, consequently, glycaemic control should improve. However, studies have also shown that, as with other therapeutic classes, there is a significant gap between results achieved in RCTs and those achieved in real-life studies. A recent comparison of data from RCTs and an administrative claims and medical records database, in which baseline HbA_{1c} ranged from 8.34–8.41%, showed that the mean change in HbA_{1c} was −1.30% in RCTs, but only −0.52% in real-world data [12]. Around three-quarters of the discrepancy was attributed to patient adherence rates, which were 29% in the real-world analysis and 95% in the RCTs [12].

In addition, studies have revealed that patients enrolled in RCTs are often not representative of real-world populations but, instead, tend to be highly selected (fewer comorbidities, more compliant, managed by selected sites to participate in trials), more motivated and better supported (financially and administratively). In one recent analysis, for instance, only 48.0% of real-life patients in the US Diabetes Collaborative Registry ($n = 182{,}525$) met the main criteria for inclusion in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study [13]. As these criteria were designed to select patients at very high cardiovascular risk, the other 52% of patients were eligible for prescription of liraglutide, but were not at high cardiovascular risk. Furthermore, in clinical care settings in northern Denmark, liraglutide users did not resemble patients included in the LEAD (Lower Educational Attainment Decision Aid) 1–5 trials, with almost three out of four routine clinical care initiators being classified as ineligible for the RCTs [14]. In yet another study, patients enrolled in T2DM trials registered at ClinicalTrials.gov were found, on average, to be younger and to have lower body mass index (BMI) scores and higher HbA1c levels than the T2DM patient population described in NHANES [15].

Thus, the present review has focused on real-life data that describe GLP1-RA treatments, and on factors such as effectiveness, tolerability, prescription patterns, adherence, persistence and cost that can influence outcomes.

Understanding endpoints: response and adherence

Response

Evaluation of treatment efficacy is an essential component of daily medical practice. Response, which is often used as an efficacy variable, is inherently arbitrary as it imparts clinical significance to effectiveness. Within the field of diabetes, the definition of response varies [16]. The 2015 UK National Institute for Health and Clinical Excellence (NICE) recommends an initial weight loss of 5–10% and a target HbA_{1c} of 6.5% (or 7.0% if the medication is associated with hypoglycaemia) [17], and also specifies targets for GLP1-RAs (HbA_{1c} decrease of 1%, body weight loss of 3%). The 2017 Francophone Diabetes Society position statement recommends individualization of objectives, with the decision to maintain or discontinue treatment after 3–6 months based on an HbA_{1c} decrease $\geq$ 0.5% and/or the achieving of metabolic targets [18].

However, as guidelines have evolved over time, the interpretation of the results of every study must now include asking whether the definition of response is clinically meaningful. In the exenatide Diabetes Therapy Utilization: Researching Changes in A_{1C}, Weight and Other Factors Through Intervention with Exenatide Once Weekly (DURATION) studies, for example, response was defined as weight loss of $\geq$ 0 kg and a decrease in HbA_{1c} of $\geq$ 0% [6,19]. In other words, any patient who lost at least 0.1 kg and/or experienced a decrease in HbA_{1c} of 0.1% was considered to have

responded to treatment. Based on this definition, > 70% of patients in these studies responded to treatment with exenatide QW. However, clearly, for some patients a response corresponded to only slight decreases in weight and/or HbA_{1c} [19], making the clinical significance of such results moot. In contrast, other studies have used definitions similar to those published in guidelines [20] or, more commonly, a long-term therapeutic goal of $HbA_{1c} < 7\%$ [21,22].

Adherence

Treatment adherence quantifies how well the treatment is maintained over time; this combines the notions of treatment observance (which describes how well a patient follows a prescription) and persistence (which describes the duration of time between starting a treatment and its discontinuation despite an ongoing prescription). Although there is no official standard or consensus on optimal levels of adherence, in general, an adherence rate $\geq$ 80% is considered sufficient for any treatment of T2DM to be effective [23], as this is associated with a decreased risk of all-cause mortality and hospitalization in such patients [24].

In real-life studies, adherence is most often assessed based on prescription or drug-dispensing data from claims databases or electronic medical records and quantified using either the medication possession ratio (MPR) or proportion of days covered (PDC) [23]. The MPR is typically defined as the number of days supplied by the prescription divided by the actual number of days between prescription refills. The PDC is a newer measure that considers the number of days covered rather than the number of days supplied [23], and is typically defined as the number of days covered divided by the actual number of days between refills. Because 'days covered' is used, a PDC cannot be > 1.0. Also, the PDC is better suited than the MPR to describe medication adherence for chronic conditions like diabetes that often require multiple medications.

Glucagon-like peptide-1 receptor agonists in real-world studies

Effectiveness and tolerability

Effectiveness and tolerability in real-life settings can be evaluated from studies that include either primary data collection or secondary analyses of data (such as claims databases, electronic medical records and existing registries). Both types of studies have limitations. Nevertheless, such studies can still provide data to evaluate long-term follow-ups (10–15 years) whereas, in RCTs, these typically last only 26–52 weeks [6,25,26]. However, long-term extensions of RCTs are generally not good sources of data, as they are often not controlled and not representative of real-world patient populations [27].

While insulin has been the gold standard for injectable medication for decades, few comparisons with GLP1-RAs have been performed in real-life settings, and these have mostly been limited to studies with exenatide, the first molecule to come to market [22,28]. From a European prospective, the observational Changes to Treatment and Outcomes in Patients with Type 2 Diabetes Initiating Injectable Therapy (CHOICE) study looked at 619 pairs of injection-naïve patients with T2DM and matching baseline data after initiation of either exenatide BID or insulin [22]. After 24 months, there were no significant differences between the two groups for mean changes in HbA_{1c} ($-1.3\% \pm 1.5$ vs. $-1.2\% \pm 1.5$, respectively) or for percentages of patients with $HbA_{1c} < 7.0\%$ (40.1% vs. 36.7%, respectively) [22]. However, patients in the exenatide BID group showed greater weight loss (-2.8 ± 6.6 vs. 1.5 ± 6.6 kg, respectively; $P < 0.0001$) and fewer hypoglycaemic events (20.3% vs. 33.3% of patients, respectively; $P < 0.0001$), but more gastrointestinal symptoms (30.8% vs. 5.9% of patients, respectively), than patients in the insulin group.

Similar results were found after analyses of US registry data collected from 2011 to 2015 [28]. In one matched cohort after 1 year of treatment with exenatide QW ($n = 1005$) and basal insulin ($n = 1944$), HbA_{1c} decreased from 8.2% and 8.4%, respectively, to 7.6% and 7.9%, respectively. In both groups, changes from baseline were most pronounced at 3–6 months. However, patients in the exenatide QW group lost a mean of 2.15 kg over the course of the year whereas, on average, patients in the insulin group lost no weight. Also, hypoglycaemic events occurred in 7.9% of patients in the exenatide QW group compared with 9.5% of patients in the basal insulin group [28].

Taken together, these real-world exenatide QW data suggest that, as with observations from RCTs [6], exenatide treatment is associated with effects on glycaemia similar to those observed with insulin, but with greater weight loss, fewer hypoglycaemic events, and higher rates of nausea and vomiting.

A number of real-world studies looked at just one GLP1-RA or at GLP1-RAs as a class, or compared different GLP1-RAs [20,21,29,30,31,32,33]. In one multicentre, observational, retrospective study, the long-term metabolic effects of exenatide BID (9 and 12 months in two cohorts) were analyzed in 299 patients with T2DM not responding to metformin and sulphonylurea at maximum dosages. In the end, 31% and 38% of patients achieved HbA_{1c} levels < 7%, with a reduction of at least 1% observed in 57% and 65% of subjects in the 9- and 12-month cohorts, respectively [34]. In the ROOTS observational study, the efficacy and safety of liraglutide was evaluated at 12 months in 245 T2DM patients with $HbA_{1c} > 7.5\%$ despite dual oral therapy. The primary composite endpoint (proportion of patients achieving an $HbA_{1c} < 7\%$ or a decrease $\geq$ 1%) was achieved in 66.5%, and the percentage of patients with HbA_{1c} levels $< 7.0\%$ and $\leq 7.5\%$ increased from 0.4% at baseline to 31% and from 3.3% at baseline to 51%, respectively [35].

In a retrospective analysis of a US electronic medical records database study (2011–2015), roughly 30% of patients reached an $HbA_{1c} < 7.0\%$ after 6 months of treatment with exenatide QW ($n = 2133$), dulaglutide QW ($n = 201$) and albiglutide QW ($n = 131$) [36]. In the prospective, multicentre Observational Study on Efficacy and Safety of Liraglutide in Subjects with Type 2 Diabetes (EVIDENCE), 3152 patients were treated with liraglutide QD [21]. At the 2-year endpoint, 29.5% of patients were still taking liraglutide and had HbA_{1c} levels < 7.0% [21].

Taken together, these real-world data underscore the fact that GLP1-RAs are effective in reducing HbA_{1c} and weight, and are also associated with a limited number of hypoglycaemias. However, when response – defined as $HbA_{1c} < 7.0\%$—is considered, the overall glycaemic control rates are still low.

A couple of retrospective analyses have looked at the impact of treatment on cardiovascular outcomes and all-cause mortality. In a study of 2006–2014 data from The Health Improvement Network (THIN) database in the UK, the 5-year risk of having a major adverse cardiovascular event was significantly lower in the group with an add-on GLP1-RA ($n = 419$; exenatide BID or QW, liraglutide QD, lixisenatide QD) vs. an add-on insulin group ($n = 1584$): adjusted hazard ratio (HR): 0.27, 95% confidence interval (CI): 0.14–0.53; $P < 0.0001$; propensity score matching of baseline characteristics [37]. In another analysis of the THIN database (2008–2015), the relative risk (RR) of all-cause mortality after a mean follow-up of 32 months was significantly lower in patients treated with a GLP1-RA ($n = 8345$; exenatide BID or QW, liraglutide QD, lixisenatide QD) vs. matched controls receiving standard treatment ($n = 16,541$): adjusted incidence rate ratio: 0.64, 95% CI: 0.56–0.74; $P < 0.0001$) [38].

Thus, these data demonstrate better cardiovascular outcomes with GLP1-RAs than with insulin, thereby suggesting that long-term mortality and morbidity endpoints may also be of value when considering treatment intensification.

Prescription patterns, persistence and adherence

Beyond efficacy, examination of prescription patterns, patient persistence and patient adherence may help physicians to better understand what to expect in their everyday practice. Patients' ability or willingness to take a medication, for instance, directly affects their glycaemic control and long-term outcomes [39,40]. In real-world settings, patient persistence and adherence to GLP1-RAs have mostly been measured using insurance and prescription databases, which contain no information on either efficacy or safety.

Persistence and prescription patterns

The rate of treatment persistence is often defined as the number of patients still taking the prescribed treatment at the end of the evaluation period, and most definitions allow for a gap in treatment, with the length of the gap tending to change with the length of the evaluation period. In insurance and prescription databases, persistence includes discontinuations ordered by a physician as well as discontinuations initiated by the patient. Some definitions also assess treatment switches with the intention to capture this physician-initiated component.

Persistence rates vary from one real-world study to the next and decrease with longer study duration (Fig. 1) [40,41,42,43,44]. In a retrospective cohort analysis of electronic medical records and national healthcare databases from six European countries (2010–2012), these data revealed that the proportion of patients undergoing treatment modification within 6 months (defined as treatment discontinuation, switch/change in therapeutic class, dose increases or off-label titration) varied significantly from country to country [41]. In a US study involving matched cohorts, switches to another antidiabetic treatment were made in 11.4% of exenatide QW patients and 6.6% of dulaglutide QW patients ($P < 0.0001$) [43]. Switches made within the GLP1-RA therapeutic class were most often to liraglutide QD, while switches made to another therapeutic class were most often to sodium–glucose cotransporter-2 (SGLT2) inhibitors.

In that study, the rate of persistence at 6 months (defined as no gap in prescription refills over > 60 days) was 51.6%, 64.4% and 72.0%/73.8% in the exenatide QW ($n = 2415$), liraglutide QD ($n = 2037$) and dulaglutide QW ($n = 2415/2037$) groups, respectively [43]. In a retrospective observational claims study of matching cohorts of patients treated with dulaglutide *vs* liraglutide ($n = 2471$) and dulaglutide vs. exenatide QW ($n = 1891$), rates of persistence at 12 months were 55% for dulaglutide vs. 43.8% for liraglutide ($P < 0.001$), and 54.9% for dulaglutide vs. 34.4% for exenatide QW ($P < 0.001$) [45]. In another recently published US matched-cohort study, rates of persistence after 6 months (defined as already described above) were 63% and 66% in the exenatide QW and liraglutide QD groups ($n = 12,306$ in both groups), respectively [42].

As with studies of persistence at 6 months, persistence rates at 12 months also varied depending on the study [40,44]. In US studies, the 12-month persistence rate (defined as no gap in treatment over ≥ 90 days) was 60% for liraglutide QD-treated patients ($n = 1321$) in one study [40], and 47% for liraglutide QD ($n = 2003$), 23% for exenatide BID ($n = 275$) and 29% for exenatide QW ($n = 883$) in another [44].

Consistent with these findings are observations suggesting high rates of treatment modification. In the CHOICE study, for example, significant changes were noted. Modifications (defined as the addition of new medication for T2DM treatment, changes in insulin schedule, discontinuation of exenatide BID or insulin initiated at baseline, or substitution of human insulin for analogue insulin or vice versa) were made in 32.2% and 29.4% of patients treated with exenatide BID and with insulin at 12 months, and in 46.1% and 39.4% of these patients at 24 months, respectively [22]. According to physicians, inadequate response and adverse events were the two most frequently cited reasons for discontinuation in the exenatide BID group, whereas inadequate response and patient choice were the most frequently cited reasons in the insulin group. These reasons for discontinuing exenatide BID are consistent with the results of a survey performed by the Adelphi Disease Specific Programme for diabetes in which physicians ($n = 443$) reported inadequate glycaemic control, nausea/vomiting and gastrointestinal side-effects as the most frequent reasons for discontinuing GLP1-RAs (exenatide BID and QW, liraglutide QD, lixisenatide QD) [46].

Adherence

Adherence rates, defined as a PDC ≥ 80% over a 6-month period, vary significantly from one real-world study to the next (Fig. 2) [42,43,47,48,49]. For exenatide BID, rates vary by 10% whereas, for exenatide QW and liraglutide QD, there is a ≥ 15% variation in adherence rates between studies. Variations are most likely due to differences in patient populations, although these are not always apparent in publications. For instance, when adherence was calculated for patients taking exenatide QW in two separate US studies, one reported 51% of patients having a PDC ≥ 80% while the other reported 38% of patients [42,43]. In another recent study, patients adherent to dulaglutide (PDC ≥ 80%) experienced greater reductions in HbA_{1c} [50].

Many studies have sought to evaluate factors influencing adherence [51]. In specific choice experiments designed to evaluate the relative importance of attributes of GLP1-RA treatments, dosing frequency and type of delivery system emerged as having significant importance in patients with T2DM [52,53]. When efficacy was assumed to be similar, patients preferred a QW dosing profile with a single-use pen or auto-injector device than a QD dosing regimen with a multiuse pen [53]. Also, patients believed that a QW dosing schedule would result in fewer missed doses than a QD schedule and, therefore, higher adherence rates [53].

Consistent with these specific choice data, in real-life studies, simpler dosing regimens appear to result in higher adherence rates. The strongest data to support this hypothesis come from studies comparing adherence to exenatide QW and exenatide BID. In a retrospective US study of administrative claims data (2012–2013) [54], adherence was 48.6% in the exenatide QW group ($n = 4041$) and 30.3% in the exenatide BID group ($n = 4586$). After adjustment in the multivariable analysis, the chances of reaching adherence rates ≥ 80% were significantly higher with exenatide QW than with exenatide BID [odds ratio (OR): 0.41] [54]. Similarly, in a recent study of US Medicare medical and pharmacy claims (2010–2013), 43.2% of T2DM patients aged > 65 years and taking exenatide QW ($n = 537$) had a PDC ≥ 80% compared with 39.0% of those taking exenatide BID ($n = 923$; $P < 0.01$) [49].

Although these data suggest that the QW formulation results in higher rates of adherence, it should be borne in mind that a patient missing a dose on a QW regimen is instructed to take the injection the next day and to resume the original schedule of injections, whereas a patient on a BID formulation who misses a dose does exactly that. Thus, with the QW regimen, the missed day is essentially invisible whereas, with the BID regimen, all missed doses are counted. In addition, in matched cohorts taking dulaglutide *vs* liraglutide ($n = 2471$) and dulaglutide *vs* exenatide QW ($n = 1891$), patients initiating dulaglutide had significantly higher proportions of adherence vs. liraglutide (51.2% vs. 38.2%,

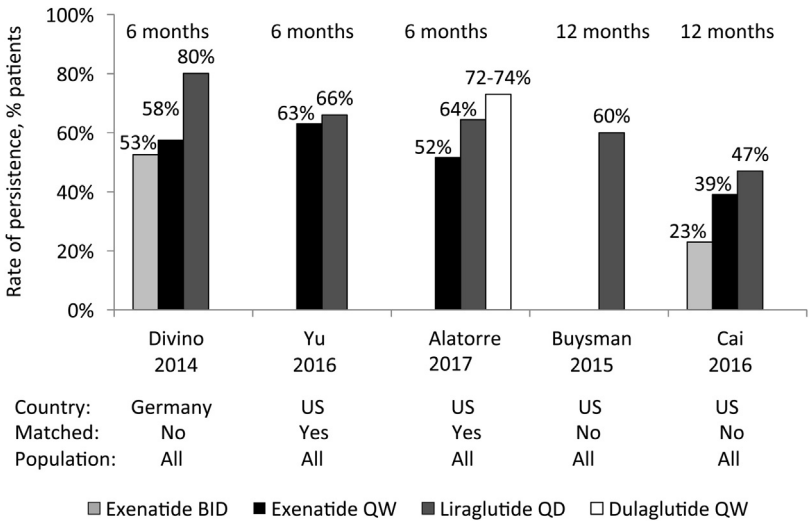

Fig. 1. Persistence rates in real-world studies demonstrate that the definition of persistence changes with study duration [40,41,42,43,44]. In the 6-month Divino study, persistence was defined as no gap over at least two prescription periods and no switch in therapeutic class. In the 6-month Yu and Alatorre studies, persistence meant no gap in prescription refills over > 60 days. In 12-month studies, persistence was defined as no gap in prescription refills over ≥ 90 days. In some studies, baseline characteristics of treatment groups were matched using propensity score matching. BID: twice a day; QD: once a day; QW: once a week; US: United States.

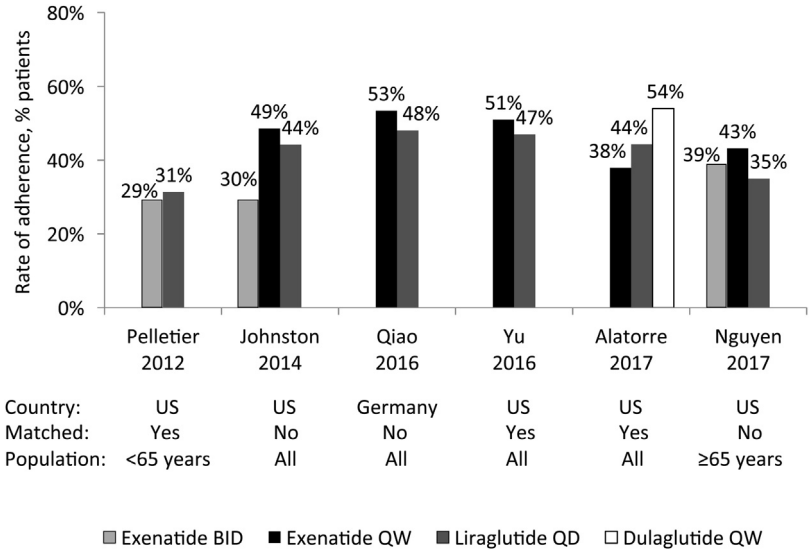

Fig. 2. Adherence in real-life studies measured over 6 months and defined as a proportion of days covered of ≥ 0.80 [42,43,47,54,48,49]. In some studies, baseline characteristics of treatment groups were matched using propensity score matching. BID: twice a day; QD: once a day; QW: once a week; US: United States.

respectively; $P < 0.001$) and exenatide QW (50.7% vs. 31.9%, respectively; $P < 0.001$) [45].

Testing the impact of delivery system on adherence is more difficult as, currently, every delivery system is associated with a different medication. Thus, adherence data comparing dulaglutide QW, delivered with a prefilled pen or syringe, and exenatide QW, which requires reconstitution (in Europe) and delivery with a pen or syringe, are likely to reflect differences in delivery system as well as differences in efficacy and tolerability. Indeed, when a US Truven Health MarketScan Research Databases analysis of 2014–2015 data studied the 6-month treatment adherence with dulaglutide QW and exenatide QW in 2415 matched pairs of patients [43], the adherence rate (PDC ≥ 80%) was 54.2% with dulaglutide QW vs. 37.9% with exenatide QW ($P < 0.0001$).

Altogether, these studies show that adherence rates are low (< 60%) and remain a significant problem with injectable therapies in daily practice. Thus, industry-driven initiatives to develop formulations with less cumbersome schedules and easier delivery systems are ongoing, and include continuous subcutaneous delivery systems to replace daily and weekly injections with miniature subcutaneous pumps that deliver medication continuously for several months [55], as well as oral formulations [56]. The main difference between subcutaneous minipumps and oral formulations is that the former would totally solve the issue of lack of adherence: once the device is implanted, the drug is delivered with no patient intervention required. However, such initiatives would need to be complemented by continuing physician–patient communication, awareness of any possible socioeconomic barriers (medication costs) and encouragement of self-care, such as following food intake and physical activity guidelines, and respecting the recommended schedule of physician visits [51].

Cost-effectiveness analyses of GLP1-RAs

Another issue that arises in everyday practice is whether the cost of treatment is worth it. Models used to quantify such considerations look at medication costs, but also disease-related healthcare costs and quality of life. Cost analyses of data collected between 1997 and 1999 showed that, for diabetes, high medication costs were offset by reductions in other medical costs, resulting in a net reduction in overall healthcare costs [57]. As for therapies related to incretins, which do not require self-monitoring of blood glucose, there is also an indirect reduction in the overall cost of treatment.

The quality-adjusted life-year (QALY) is now an accepted measure for economic evaluations that assess the monetary value of medical interventions. This generic measure of disease burden describes a year of life in terms of its quality: a year in perfect health has a QALY = 1; a year in ill health has a QALY < 1. In the UK, NICE estimates that £30,000 (€34,000) per QALY gained is an acceptable cost and uses this amount as a willingness-to-pay cut-off point [58]. In France, the willingness-to-pay threshold has not been formally defined, although the €34,000 used in the UK is often used as a reference [59].

Recently, several studies have compared the cost of GLP1-RAs using models that include an analysis of QALYs gained [59,60,61]. In a 2016 network analysis of data from 6677 T2DM patients inadequately controlled with metformin alone (14 different trials lasting at least 24 weeks), the cost of GLP1-RA treatment in the UK over a lifetime horizon of 40 years was £19,930 for exenatide QW, £19,903 for dulaglutide QW, £19,192 for lixisenatide QD, £19,827 for liraglutide 1.2 mg QD and £22,016 for liraglutide 1.8 mg QD [62]. Although exenatide QW treatment was associated with a larger QALY gain per patient than the other treatments, the cost per QALY gained with exenatide QW was £596 more than with dulaglutide QW, £1004 more than with liraglutide 1.2 mg QD and £10,002 more than with lixisenatide QD. On the other hand, the cost per QALY gained was lower with exenatide QW than with liraglutide 1.8 mg QD.

Thus, the authors concluded that, assuming a willingness-to-pay threshold of £20,000 (€23,000), the probability that exenatide QW would be cost-effective ranged from 76–99% across all comparisons. However, these results were published before some reports of cardiovascular outcomes trials with GLP1-RAs, making it now necessary to re-analyze the cost-effectiveness of GLP1-RAs between themselves and against active comparators on the basis of cardiovascular protection with some antidiabetic drugs. In other words, such studies of cost-effectiveness analyses should now certainly take into account the number of cardiovascular events avoided.

In another network meta-analysis in which the cost model was calculated within the French national healthcare setting, the cost of GLP1-RA treatment over a lifetime horizon of 40 years was €41,562 for dulaglutide QW and €43,021 for exenatide QW [59], with the former associated with a larger QALY gain per patient than the latter. Assuming a willingness-to-pay cut-off of €30,000, the probability that dulaglutide QW would be considered cost-effective *vs* exenatide QW was 99.5%. Thus, the authors concluded that treatment with dulaglutide QW was more advantageous than treatment with exenatide QW.

While such discrepant conclusions are certainly partly due to country-specific differences in costs, they are also likely to be related to differences in models used, choice of population characteristics and treatment effects. Nevertheless, even though model specifics are likely to skew results in favour of one medication over another, the overall results reveal that treatment with GLP1-RAs is cost-effective and well below the willingness-to-pay cut-off of €20,000–30,000.

Conclusion

In daily practice, treatment success has to be measured by multiple criteria, including efficacy, tolerability, treatment persistence, treatment adherence and patient satisfaction. While guidelines and prospective clinical trials can help to guide decisions about treatment initiation, it is real-life studies that provide data on long-term effectiveness. In addition, considering the cost of GLP1-RAs, regular re-evaluation of treatment is necessary and should include the concept of QALYs gained.

Disclosure of interest

Bruno Guerci has been an advisory panel/board member for Sanofi, Eli Lilly, Novo Nordisk, Servier, Novartis, GSK, MSD, Boehringer Ingelheim, AstraZeneca, Abbott, Medtronic and Roche Diagnostics, and a clinical investigator for Sanofi, Eli Lilly, Novo Nordisk, Servier, GSK, BMS, AstraZeneca, Medtronic, Abbott, Roche Diagnostics, MSD, Novartis, Janssen and Boehringer Ingelheim; he has also received research support from Medtronic, Vitalaire, Sanofi, Eli Lilly and Novo Nordisk.
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Hélène Hanaire participated in advisory boards or symposia for Abbott, Lilly, Medtronic, MSD, Novo Nordisk, Roche Diabetes Care, Sanofi-Aventis, Servier, Vitalaire
M. Marre participated in boards for Abbott, Intarcia, MSD, Novo Nordisk, Sanofi and Servier; received speaker fees from Abbott, Eli Lilly, MSD, Novo Nordisk, Sanofi and Servier; and received research support from MSD, Novartis, Novo Nordisk, Sanofi and Servier.
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