Brief report

GLP-1 agonist treatment: Implications for diabetic retinopathy screening

Lakshminarayanan Varadhan a, Tracy Humphreys a,b, Christian Hariman a, Adrian B. Walker a, George I. Varughese a,*

a Department of Diabetes and Endocrinology, University Hospital of North Staffordshire NHS Trust, Springfield Unit, North Buildings, Stoke-on-Trent ST4 6QG, United Kingdom
b Department of Ophthalmology, University Hospital of North Staffordshire NHS Trust, Springfield Unit, North Buildings, Stoke-on-Trent ST4 6QG, United Kingdom

Article history:
Received 2 August 2011
Accepted 16 August 2011

Abstract presented as an oral presentation at the 71st Annual Scientific session of the American Diabetes Association in San Diego, USA on 26th June 2011
(Reference: 137-OR)
Published on line 8 September 2011

Keywords:
GLP-1 agonist
Retinopathy
Screening

ABSTRACT

Rapid improvement in glycaemic control induced by GLP-1 agonist therapy could be yet another illustration of transient or permanent progression of diabetic retinopathy, similar to documented examples such as pregnancy and continuous subcutaneous insulin infusion. Specific guidelines would be needed to monitor this paradoxical phenomenon during treatment with GLP-1 agonists.

© 2011 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

GLP-1 agonist therapy is used extensively for the treatment of patients with type 2 diabetes (T2DM) and its efficacy and sustainability have been well documented [1,2]. Rapid improvement in glycaemic control could cause progression of diabetic retinopathy (DR) – clinical situations being pregnancy, intensive insulin therapy or insulin pump therapy

[3–7]. A case report reported similar phenomenon with Exenatide treatment [8]. Increase in IGF-1 levels and retinal ischemia have been the proposed pathologic aetiology [9–11]. Retinal screening in the UK is performed locally by community optometrist based on 2 × 2 digital photographs, guided by set protocols for frequency of screening and referral to hospital ophthalmologists, from the National Screening committee [12]. The aim of our study was to analyse the impact of rapid improvement of glycaemic control with

* Corresponding author. Tel.: +44 1782 553425; fax: +44 1782 553427.
E-mail address: george.varughese@uhns.nhs.uk (G.I. Varughese).
0168-8227/– see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.diabres.2011.08.017
Exenatide treatment on DR status in patients with T2DM and its implication for DR screening (Liraglutide was not available for clinical use during this study period).

2. Material and methods

A retrospective analysis of patients on Exenatide treatment was performed.

2.1. Inclusion criteria

- Exenatide for >6 months.
- HbA1c: At least one reading pre-Exenatide initiation and readings at 3 and 6 months post-initiation (9, 12 months and beyond if continuing treatment).
- Retinal images: one dataset pre-Exenatide; repeat DR data at least 3 months after Exenatide initiation.

HbA1c reading available closest to the DR screening was taken for analysis. Retinal images were acquired from community and hospital screening images and classified as background (R1), pre-proliferative (R2) and proliferative (R3), with coexistent maculopathy (M1) or photocoagulation (P1). Development of new DR, worsening of DR grades in either eye, development of maculopathy or need for photocoagulation was considered as progression of DR.

3. Results

Of the 325 Exenatide-treated patients on our database, 165 patients satisfied the inclusion criteria. Mean age was 56.3 years (range: 27–75). 56.4% were males. Mean duration of diabetes was 12 years (range: 1–32). Mean HbA1c at baseline was 9.6% (81 mmol/mol); median 9.4% (79 mmol/mol); range 6.3–14.2% (45–132 mmol/mol). 58.8% of the patients had baseline evidence of DR. 19.4% failed to achieve any reduction in HbA1c after initiation of Exenatide. Mean lowest HbA1c achieved was 7.9% (63 mmol/mol); median 7.8% (62 mmol/mol); range 5.7–13.1% (39–120 mmol/mol). Mean reduction in HbA1c was 1.9% (21 mmol/mol); median 1.5% (16 mmol/mol); range 0.1–6.4 (1–70 mmol/mol) in mean duration of 264 days (median 297; range 90–747). Repeat DR screening was done after a mean duration of 234 days (median 216; range 90–617).

In the overall cohort, 49 of the 165 patients (29.7%) had progression of DR (new onset 16; progression of pre-existing DR 33) in comparison to 19.4% in whom DR improved (p < 0.005). The deterioration was noted despite the ‘progressors’ having better blood pressure control and comparable renal function and lipid profile before and after Exenatide initiation. Of the 133 patients who had a reduction in HbA1c, 47 (35.3%) had worsening of DR compared to 17.3% whose DR improved (p < 0.001). The proportion of patients showing progression of DR was significantly higher in patients who had a reduction in HbA1c compared to those who had worsening of glycaemic control (35.3% vs. 6.2%; p < 0.001).

4. Discussion

Our pilot study demonstrates the substantial risk of progression of DR with significant improvement of glycaemic control with Exenatide. These results could be applicable to rapid improvement in glycaemic control with any GLP-1 agonist therapy. The paradox of improvement in glycaemic control and worsening of DR is well recognized but less commonly perceived in routine clinical practice. Although there are guidelines for trimester based screening during pregnancy in the UK, these are not usually extrapolated to such clinical situations [13].

In our cohort, 49/165 patients had progression of DR, of whom 47 (96%) had an improvement in HbA1c. The proportion of patients with progression of DR was higher, with greater reductions in HbA1c (0% to –2% (0 to –21 mmol/mol): 30.1%, –2% to –4% (–22 mmol/mol to –43 mmol/mol): 43.6%, >–4% (–43 mmol/mol): 45.5% (Table 1). The table also shows that for any degree of reduction in HbA1c, the proportion of patients with progression of DR was higher than those in whom DR improved. All these data point towards a potential direct causal effect of HbA1c reduction due to Exenatide, with worsening DR.

We acknowledge that a retrospective study design is not ideal to predict variable for ‘progressors’, this sub-group had

| Table 1 - Changes to diabetic retinopathy based on HbA1c reduction. |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                          | HbA1c | 0 to <–2% (0 to ≤21 mmol/mol) | HbA1c | –2 to ≤4% (–22 to ≤43 mmol/mol) | HbA1c | >–4% (greater than 43 mmol/mol) | Total with HbA1c ↓ | HbA1c↑ Worsened |
| No DR to new DR          | 5 (6.0%) | 7 (18.0%) | 3 (27.3%) | 15 (11.3%) | 1 (3.1%) |
| DR worsening             | 20 (24.1%) | 25 (25.6%) | 8 (18.2%) | 54 (24.0%) | 4 (1.8%) |
| Total: DR progressing    | 25 (30.1%) | 17 (43.6%) | 8 (21.2%) | 47 (35.3%) | 6 (1.8%) |
| DR static                | 17 (20.5%) | 7 (18.0%) | 1 (23.7%) | 26 (19.6%) | 2 (1.8%) |
| No DR to No DR           | 22 (26.5%) | 12 (30.8%) | 2 (9.0%) | 37 (27.8%) | 15 (46.9%) |
| DR improved              | 19 (22.9%) | 3 (7.6%) | 1 (9.0%) | 23 (17.3%) | 9 (28.1%) |
| Total: DR static/improved| 58 (69.9%) | 22 (56.4%) | 6 (54.5%) | 86 (64.7%) | 30 (93.8%) |
| Total                    | 83 (100%) | 39 (100%) | 11 (100%) | 133 (100%) | 32 (100%) |

| ↓ denotes reduction, ↑ denotes increase. |
significantly higher baseline HbA1c. They were also older and had greater mean reduction in HbA1c (both not significant) and comparable glycaemic control post-Exenatide (Table 2). The proportion of patients with pre-existent DR was higher among the ‘progressors’ (67.3% vs. 54.2%, p = not significant). The greater the progression of DR through various grades, the higher was the HbA1c reduction achieved – HbA1c reduction by −1.9% in patients with retinal score progressing by 1 grade compared to −2.9% in patients with retinal score progressing by >3.

There are limitations to this study. Firstly, a prospective randomized study with time-matched and frequent HbA1c and retinal screening is required to address this issue. Secondly, long term follow up data is not available to document whether DR worsening is temporary or permanent [14]. Long-term studies have shown this phenomenon to be transient and inconsistent; eventually good glycaemic control on the long run improves microvascular outcomes albeit such deterioration in the early stages of treatment [15,16]. The purpose of our study however, was to emphasize the need for screening rather than monitoring the outcome. Thirdly, though formal grading for retinal images would be ideal; such as the Early Treatment of Diabetic Retinopathy Screening grading (ETDRS), our database was based on local screening committee guidelines.

<table>
<thead>
<tr>
<th>Table 2 – Comparison between ‘progressors’ and ‘non-progressors’ of diabetic retinopathy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressors</td>
</tr>
<tr>
<td>N=</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Duration</td>
</tr>
<tr>
<td>Baseline HbA1c</td>
</tr>
<tr>
<td>% insulin treated</td>
</tr>
<tr>
<td>Pt with HbA1c &lt; 7.0%</td>
</tr>
<tr>
<td>Mean lowest HbA1c</td>
</tr>
<tr>
<td>Reduction in HbA1c</td>
</tr>
<tr>
<td>% with DR at base</td>
</tr>
</tbody>
</table>

* P value not significant.
· P < 0.05.

5. Conclusion

This ‘proof-of-concept’ retrospective analysis shows that a significant proportion of patients treated with Exenatide, who have rapid improvement in HbA1c may be at risk of development or progression of DR. The longer the duration of diabetes, presence of pre-existent DR and greater reduction in HbA1c seem to be the predictors of such deterioration. This important complication could be overlooked if we solely rely on the annual retinal screening schedule. Further prospective studies are required to develop guidelines for more frequent monitoring of retinal status in patients who are treated with GLP-1 agonists.

Disclosure

None.

Author contributors

LV, TH and CH collected the data. LV analysed the results, wrote the manuscript and researched data. LV and TH were involved in collating the retinal screening grades. TH has directly contributed to grading the digital images as well as quality assurance assessments and also ran some of the Exenatide initiation sessions for these diabetic patients. CH set up the initial database. ABW contributed to the discussion, edited the manuscript and was instrumental in setting the protocols for the initiation and continuation of Exenatide treatment. GIV proposed the initial plan and outline for the study, researched data and contributed to the discussion.

Acknowledgments

The Clinical Nurse Specialists in Diabetes (Mrs. Ann Shelley-Hitchen, Mrs. Sarah Taylor, Mrs. Julie Wilkins and Mrs. Melita Yelland) for their help in gathering information for setting up the database and also running the Exenatide group-start sessions for these patients.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES


