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Case Report

Intervention of Type 2 Diabetes With GLP-1RA Caused Early Worsening and Remission of Diabetic Retinopathy

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Abstract

In the post-hoc analysis of Sustain-6, semaglutide increased early worsening (EW) of diabetic retinopathy (DR) in patients recruited to the study. We report a case of type 2 diabetes complicated with EW of DR, treated with continuous short acting lixisenatide followed by exenatide twice a day. A 43-year-old man diagnosed as overt type 2 diabetes with 10.7% of HbA1c having two-year history with obesity was treated with lixisenatide and switched to exenatide. After strict control by GLP-1RA and metformin, OCT confirmed the development of macular edema. He was treated with Ranibizumab injection and remission of macular edema was recognized after 1 year under the continuous treatment with exenatide. This case supports the notion that EW can occur in both types of diabetes mellitus and be a phenomenon associated with the rapidity and magnitude of improvement in glycemic control by GLP-1RA regardless of the use of insulin. Our case also exhibited remission from EW under continuous strict control by short acting GLP-1RA and assured the effect of ranibizumab on macular edema observed in EW.

Keywords: Diabetic retinopathy, Early worsening, GLP-1 receptor agonist, Exenatide, Ranibizumab

Introduction

Large-scale clinical studies on GLP-1 receptor agonists (GLP-1RAs) have made it possible to lucidly rank GLP-1RAs according their effects in improving parameters such as body weight, blood pressure and blood glucose as well as on CV events and to collect statistics on adverse events [1,2]. Among them, Sustain-6 study attained significant reduction in CV events, whereas semaglutide increased the early worsening of diabetic retinopathy (DR), particularly in patients who had pre-existing DR and poor glycaemic control at baseline [3]. Early worsening of DR has been identified as an adverse event in insulin-treated patients in clinical trials such as the DCCT [4] and Kroc study [5], studies which showed rapid reductions of blood glucose and HbA1c in type 1 diabetes patients. In Sustain-6, the first large scale trial to identify early worsening of DR in type 2 diabetic patients, semaglutide brought about a higher rate of DR, albeit marginally [6], particularly in patients undergoing baseline insulin therapy. Here we report a case of type 2 diabetes with a complication of early worsening of DR treated by continuous short-acting lixisenatide, followed by exenatide twice a day.

Case

A 43-year-old man complaining of diplopia was referred to our hospital by a nearby ophthalmologist for a suspected oculomotor nerve disorder (diabetic cranial neuropathy) associated with simple diabetic retinopathy. He was diagnosed with overt obese type 2 diabetes with a two-year history of HbA1c levels above 10.7% (max BMI 37.2). The prescribed treatment was temporary insulin to relieve glucose toxicity, followed by add-on therapy with lixisenatide (20mg/day). An ophthalmologic examination revealed hard exudate (HE) and dot haemorrhaging, but no macular oedema at baseline. HbA1c gradually fell in the course of follow-up, reaching 5.8%, a level sufficiently low to merit cessation of insulin therapy, at 3 months. Mixed meal tests performed along the course of lixisenatide administration (baseline, 3rd day, and 6 months) exhibited sustained improvement of pre- and postprandial glucose without insulin augmentation as evidenced by AUC of CPR (511ng min/ml, 464ng min/ml, and 335ng min/ml, respectively). GLP-1 therapy was continued and treatment with lixisenatide was switched to exenatide to attain further body weight reduction, along with the addition of 1000mg of metformin. In response to the treatment of 1 year, his BMI fell from 34.3 at the first visit to 31.3 (9% reduction). Eighteen months later his HbA1c levels were consistently under 6%, and a repeat fundoscopy revealed circular aggregation HE with nearby macula without any optical symptoms. Optical coherence tomography (OCT) confirmed the

development of macular oedema under treatment with only GLP-1RA and metformin. The patient was administered an injection of ranibizumab, and 1 year of continuous treatment with exenatide resolved the macular oedema and reduced HbA1c to below 6%.

Discussion

In population-based analysis, it has been indicated that the use of GLP-1RA is associated with an overall reduced risk of diabetic retinopathy compared to insulin despite a transient increased risk by 44 % observed in GLP-1RA treatment compared to 2 or 3 oral agents [7]. A post hoc mediation analysis of the Sustain-6 study Vilsbøll T [3] also suggested that the increase in DR seen with semaglutide compared to placebo may be associated with the large and rapid decline in HbA1c levels during the first 16 weeks of treatment. Furthermore, most of the patients who suffered DR events had received prior chronic insulin treatment in conjunction with semaglutide add-on therapy. While early worsening of DR has been observed in insulin-treated patients, primarily those with type 1 diabetes, data from the DCCT suggests that early worsening of DR results from the rapidity and magnitude of improvement in glycaemic control with insulin [4,5]. In Sustain-6, the addition of semaglutide reduced body weight and HbA1c rapidly and eminently regardless of chronic insulin administration [6]. However, the most patients who suffered from early worsening of retinopathy were under chronic insulin therapy. The agents given to our patient, insulin to relieve glucose toxicity at the initial phase followed by lixisenatide or exenatide and metformin without insulin, appeared to be contributing therapy for early worsening of DR associated with type 2 diabetes. Regarding the mechanism, involvement of insulin effect, partly through IGF-1 signaling [8] would be limited as this patient exhibited insulin reduction along with GLP-1RA treatment. Diabetic retina expresses lower level of GLP-1, while the expression of GLP-1R is retained [9]. Meanwhile, the expression of GLP-1R in the retinal ganglion cell layer [10], where VEGF and insulin receptor are also expressed [11], might either precipitate or inhibit the development of early worsening of DR. As to permeability of retina, GLP-1RA acts protectively to the breakdown of blood-retinal barrier [12]. As reported by DCCT and Sustain-6, clinical observational analysis has indicated a certain association between the early worsening of DR in both types of diabetes mellitus and how quickly, and the degree to which, glycaemic control improves. The DCCT, on the other hand, demonstrated an amelioration of retinopathy through strict control with intensive insulin therapy. Our case exhibited a similar remission from early worsening of DR under continuous strict control via a short-acting GLP-1RA, confirming the effect of ranibizumab on the macular oedema observed in early worsening of DR. Moreover, our case confirmed the efficacy of ranibizumab on the macular edema even associated with early worsening of the retinopathy.

Compliance with Ethical Standards

Disclosure of potential conflict of interests, Dr. Shiba reports grants and personal fees from Mitsubishi Tanabe Pharma, grants and personal fees from Daiichi Sankyo Company Limited, grants and personal fees from ONO PHARMACEUTICAL CO., LTD., personal fees from Eli Lilly Japan K.K., personal fees from Boehringer Ingelheim, personal fees from Merck Sharp & Dohme (MSD), personal fees from Novartis Pharma, personal fees from Novo Nordisk Pharma Ltd., outside the submitted work. The other authors declare no conflict of interests.

Human Rights Statement and Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

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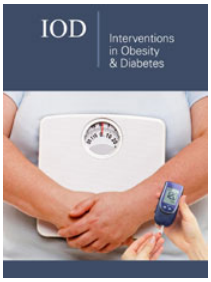

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