

Pioglitazone Associated Diabetic Macular Oedema

The Editor,

Sir,

Thiazolidinediones are frequently prescribed oral medications that effectively reduce insulin resistance in Type 2 diabetic patients (1). According to clinical studies, fluid retention and peripheral oedema are reported in 5–7% of patients using glitazones, rising to 15% of patients using pioglitazone with insulin (2). This fluid retention can aggravate diabetic macular oedema (DME) and complicate its management (3). We describe a patient who developed focal DME after pioglitazone had been used.

A 57-year old Caucasian female who had a history of Type 2 diabetes mellitus for 17 years presented to the ophthalmology department with a one-month history of gradual loss in visual acuity (VA) in her right eye. At presentation, her glycosylated haemoglobin (HbA_{1c}) was 48 mmol/mol (6.5%) and her blood pressure was 120/75 mmHg. Her medications included pioglitazone, metformin, gliclazide and aspirin. Pioglitazone (45 mg/day) treatment which reduced her HbA_{1c} level from 97 mmol/mol (11%) to 48 mmol/mol (6.5%) within six months had been started nine months previously and since its use, the patient reported gaining weight, increasing from 75 kg to 88 kg. She also complained of pitting peripheral oedema, predominantly involving both lower extremities. No microalbuminuria was diagnosed either from a 24-hour urine collection or in a spot sample. On ophthalmic examination, her best corrected visual acuity (BCVA) was 2/10 in the right eye (OD) and 10/10 in the left eye (OS). On optical coherence tomography (OCT 3) [Carl Zeiss Meditec, Inc, Dublin, California], hyporeflective focal intrafoveal cyst and central retinal swelling were observed in both eyes (341µ OD, 313 µ OS). Her BCVA was 10/10 in both eyes a year before starting pioglitazone, and DME or pre-proliferative retinopathy was not present before the pioglitazone treatment.

Because there had been reports of adverse effects of pioglitazone on developing DME but her HbA_{1c} level was 48 mmol/mol (6.5%), we referred the patient to the endocrinologist. In consultation with the endocrinologist, it was recommended that pioglitazone should have been stopped; however, pioglitazone could not be stopped because she refused to use insulin syringes or needles every day instead of taking pioglitazone orally. In such a case, we decided to use bevacizumab (BVC) [Avastin, Genentech, South San

Francisco, California] based on its ability to depress DME and its availability. Approval was obtained from the institutional review board for the off-label use of BVC for this situation. After an explanation was given about the purpose and potential adverse effects of the procedure, the patient agreed to receive intravitreal injection of BVC and informed consent was obtained from her. One month after the first injection, her VA improved to 8/10 in her right eye and central macular thickness (CMT) reduced in both eyes (307µ OD, 269µ OS). These significant changes continued throughout the three-month follow-up. Three months after the injection, her CMT and VA worsened again (BCVA: 2/10 OD 10/10 OS and CMT: 301µ OD 315µ OS). Therefore a second injection was given to each eye. One month after the second injection, her VA improved to 4/10 in her right eye and CMT reduced in both eyes (264µ OD, 253µ OS). Best corrected visual acuity in her right eye did not increase compared to the first injection due to cataract progression. The patient had two intravitreal injections of BVC 1.25 mg in 0.05 ml to each eye. No systemic adverse events were observed. After these injections, she appeared to understand her condition and the risks of pioglitazone treatment; the pioglitazone was discontinued. Fourteen units of insulin glargine (Lantus®, Sanofi Aventis) given once daily, were prescribed to maintain glycaemic control after the cessation of pioglitazone. She required no laser photocoagulation therapy. Two months after withdrawal of pioglitazone, the patient reported a reduction in her peripheral oedema and weight loss of 7 kg (weight 81 kg). Her HbA_{1c} was 53 mmol/mol (7%). Her right BCVA improved to 10/10 with cataract surgery, performed at nine months after the beginning of insulin treatment. The patient was followed for nine months after the surgery and no recurrence of DME was observed.

These drugs should be used with caution in patients with DME. Patients using the drug should be advised to seek immediate medical attention if they begin to experience visual symptoms. Routine prescheduled intravitreal injections may not be appropriate in the primary treatment of patients with glitazone associated DME and the decision should be individualized in each patient. If it is possible, cessation of the drug before performing an interventional management and prescription of another anti-diabetic agent is the best choice for the primary treatment. Intravitreal BVC injection may provide an alternative and effective treatment option in such cases.

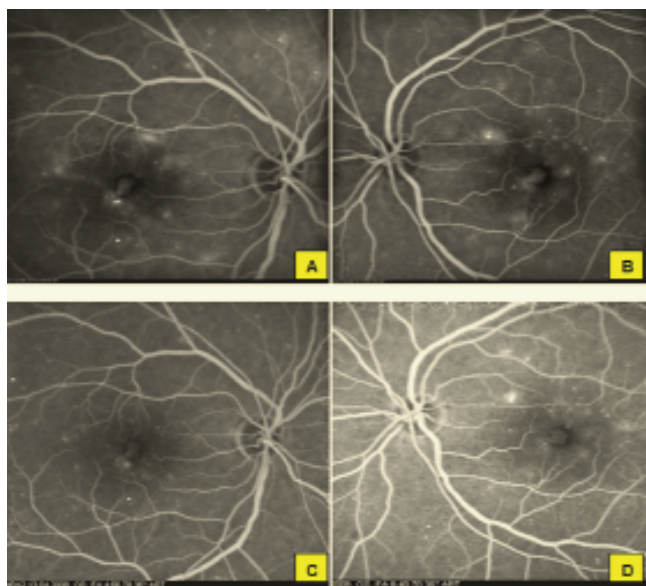


Fig. 1: A, B: Late-phase fluorescein angiogram of both eyes showing leakage around the perifoveolar capillary network before the first injection. C, D: Reduced leakage one month after the first injection.

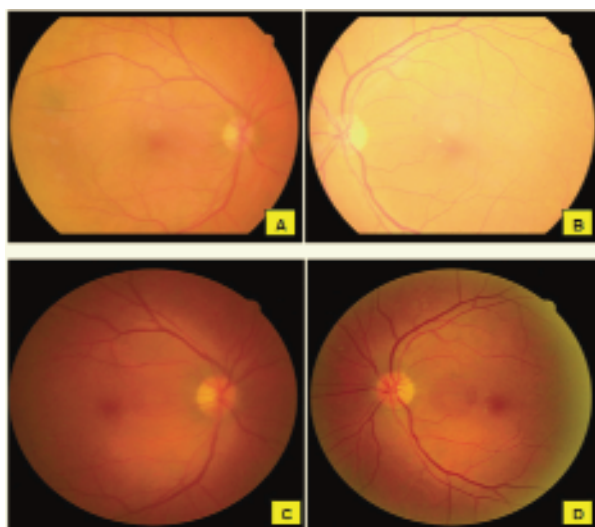


Fig. 2: A, B: Photograph of right eye one month after the second injection; visual acuity (VA): 4/10; C: Photograph of right eye three months after the second injection; VA: 4/10; D: Photograph of left eye one month after the second injection; VA: 10/10; E: Photograph of left eye three months after the second injection; VA: 10/10.

From: G Gokce¹, AH Durukan², FC Erdurman², OM Ceylan², G Sobaci²

¹Department of Ophthalmology, Sarikamis Military Hospital, Kars, Turkey and ²Department of Ophthalmology, Gulhane Military Medical Academy, Ankara, Turkey.

Correspondence: Dr G Gokce, Department of Ophthalmology, Sarikamis Military Hospital, Kars, Turkey.
E-mail: drgokcengokce@gmail.com

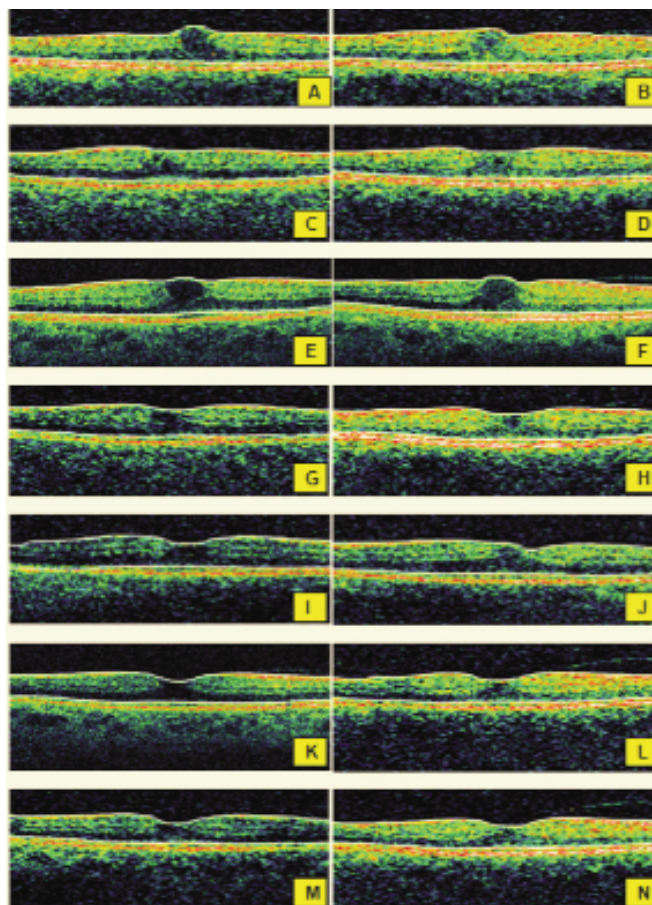


Fig. 3. Optical coherence tomography. A, B: Hyporeflective focal intrafoveal cyst and central retinal swelling were observed in both eyes (341μ OD, 313μ OS) at presentation. C, D: One month after the first injection (307μ OD, 269μ OS). E, F: Three months after the first injection CMT worsened again (301μ OD, 315μ OS). G, H: One month after the second injection (264μ OD, 253μ OS). I, J: Three months after the second injection (247μ OD, 292μ OS). K, L: One month after the cessation of pioglitazone treatment (255μ OD, 245μ OS). M, N: Five months after the cessation of pioglitazone treatment (231μ OD, 242μ OS).

REFERENCES

1. Ryan E, Han D, Ramsay R, Cantrill H, Bennett S, Dev S et al. Diabetic macular edema associated with glitazone use. *Retina* 2006; **26**: 562–70.
2. Niemeyer NV, Janney LM. Thiazolidinedione-induced edema. *Pharmacotherapy* 2002; **22**: 924–9.
3. Perkovich BT, Meyers SM. Systemic factors affecting diabetic macular edema. *Am J Ophthalmol* 1988; **105**: 211–12.