Sir,

Anti-VEGF (vascular endothelial growth factor) drugs in diabetic macular oedema

I read the article by Forte *et al*[1] with interest. I congratulate the authors for evaluating different treatment options in diabetic macular oedema (DME).

I would like to comment about the treatment of DME with intravitreal bevacizumab (IVB) alone. The half-life of IVB in the vitreous cavity of a rabbit eye has been shown to be 4.32 days.[2] Most *in-vivo* studies have shown that IVB either plateaus or decreases macular thickness in most eyes between 3–6 weeks. This demands a need for repeat injections.

According to Parravano *et al*,[3] multiple studies have shown only short-term benefit of anti-VEGF (vascular endothelial growth factor) drugs as compared with present treatment modalities. There is no sufficient high-quality evidence from large randomized controlled trials supporting the use of either single or multiple anti-VEGF intravitreal injections to treat DME.

The systemic safety of IVB is not yet established. Bevacizumab has the potential to inhibit the important physiological functions of VEGF, such as wound healing and development of collaterals deemed significant in myocardial or peripheral ischaemia, thus potentially causing systemic adverse events.[4]

Regarding intravitreal steroid as an adjunct has also shown a temporary effect on macular oedema, with no long-term benefit on visual acuity, but being associated with side effects. The studies have not shown any additional benefit of intravitreal steroid over laser photocoagulation.[5]

In conclusion, anti-VEGF or steroid can be used in gross macular oedema as an adjunct for short-term benefit, to reduce the macular thickness, followed by focal or grid laser to give a sustained response. Macular laser photocoagulation is still the gold-standard treatment. Multi-centre controlled trials are needed to compare IVB alone and in combination with laser photocoagulation in DME, to assess the long-term benefit and safety, the number of injections needed for maintenance of the effect, and the associated risk.

Conflict of interest
The author declares no conflict of interest.

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Sir,

Reply to Chhablani

We thank Dr Chhablani[1] for his interest in our article[2]; we evaluated diffuse diabetic macular oedema and obtained good functional and anatomic results during a follow-up of 12 months after treatment with intravitreal bevacizumab, when compared with the combination of intravitreal triamcinolone and laser photocoagulation. We agree that intravitreal bevacizumab lacks in large randomized controlled trials and could be used in case of gross macular oedema in order to reduce macular thickening, followed by laser photocoagulation. The latter remains indeed the gold standard for diabetic macular oedema.

Conflict of interest
The authors declare no conflict of interest.

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Sir,

Reply to Yip *et al*

We read with great interest the paper by Yip *et al*[1] concluding that laser peripheral iridotomy (LPI) for

primary angle closure (PAC) is not independently associated with cataract progression.

The authors mention that cataract surgery may be an alternative treatment for occludable angles, potentially addressing both PAC and cataract blindness with one procedure. The potential complications from intraocular surgery, though, are greater than those from LPI. However, LPI has complications such as intraocular haemorrhage and inflammation, intraocular pressure (IOP) spikes, glare, diplopia, and corneal damage. These are primarily not sight threatening, but have to be always taken into consideration.

Another potential complication is cataract formation, and this has been extensively reviewed by Yip *et al*. Despite their conclusion, there is still some controversy on this matter, with some authors supporting the opposite.[2,3] Thus, one must always be aware of such a theoretical risk after LPI. Except for the disturbances in aqueous flow in patients undergoing LPI, we suggest that, using higher-energy settings, inaccurate focusing of the laser beam, excessive or undertreated post-LPI uveitis, previous intermittent angle-closure episodes with IOP elevation, and other anatomical parameters, yet to be recognised, could be considered as possible stimuli of crystalline lens disturbance with consequent opacification.

A potential complication of Nd:YAG LPI was reported by us recently.[4] This involves damage to the zonules with subsequent dehiscence during routine phacoemulsification cataract surgery, affecting an otherwise healthy female with narrow angles. Our paper includes reports suggesting the same effect of LPI (both with Nd:YAG and with argon lasers), resulting in spontaneous dislocation of the crystalline lens.[4] We suggested that Nd:YAG LPI may be regarded as an isolated risk factor for structural zonular damage and instability of the crystalline lens, and appropriate precautions should be taken during intraocular surgery. Regardless of the opacification being the result of the LPI, age-related or of any other cause, zonular damage could have considerable implications in subsequent cataract surgery, especially in cases where the zonules are already compromised, such as in pseudoexfoliation syndrome, previous ocular trauma, and congenital systemic diseases like Marfan's syndrome.[5]

Considering the large number of patients who would potentially benefit from prophylactic LPI, potential adverse sequelae of such a procedure must not be underestimated. More specifically, the possibility of cataract progression and zonular instability after LPI has important implications for patients at risk of angle closure. Choosing between primary cataract surgery and LPI is the main consideration in such cases. The therapeutic approach should be individualised and treatment benefits must always be balanced against eventual complications.

Finally, we would like to congratulate the authors for their excellent contribution on a very important field of ophthalmology.

Conflict of interest
The authors declare no conflict of interest.

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Sir,

Reply to Athanasiadis *et al*

We are grateful to Dr Athanasiadis *et al*[1] for their interest in our manuscript,[2] and for this opportunity to reiterate the points made therein.

Zonular disruption during laser peripheral iridotomy (LPI) can occur if sufficient energy is applied or if there is pre-existing zonular weakness. Indeed, Nd:YAG laser zonulotomy and hyaloidotomy are used in the management of some cases of aqueous misdirection syndrome. However, in our experience from the specialist angle-closure clinic at Moorfields City Road, the Zhongshan Angle-closure Prophylaxis (ZAP) study in Guangzhou, China (ISRCTN45213099), and our research programme in Mongolia, culminating in over 4500 LPIs and 800 phacoemulsification procedures in the same pool of patients, we have not encountered this problem with LPI.

Dr Athanasiadis's case report[3] omits to mention where the initial phaco wound was (ie superior or temporal). This may have some bearing on the location of the dehiscence. The report also does not mention the power and number of shots during LPI. We were puzzled as to why two iridotomies were performed in each eye of the patient reported in this case. One adequately sized iridotomy is sufficient in management of angle closure.

Angle closure is known to affect people with a variety of genetic mutations that cause zonular abnormalities and weakness as part of their phenotype: PXF, FBN1 (Marfan and Weill Marchesani syndromes), lysyl hydroxylase (Ehler Danlos VI), MTHFR