Author's response to reviews

Title: The case for intraocular delivery of PPAR agonists in the treatment of diabetic retinopathy

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Author's response to reviews: see over
1st August 2012
Dear Dr. Holmes,
Thank you for providing us with the reviewer’s comments. We have studied them carefully and believe that we have now addressed the matters for revision. Below we outline how we have addressed them point-by-point. With respect to the editorial points raised, we have indicated that Maxwell Treacy is the corresponding author.

Reviewers’ comments:
Chirag Shah’s review: there are two key points under the ‘discretionary revisions’:
1. They should temper their predictions for the future given that if such intravitreal agents were developed, it is very possible they could not be administered with anti-VEGF agents within the same syringe (e.g., if the solutions precipitated when mixed), or perhaps anti-VEGF agents will not be necessary in the absence of macular edema, or perhaps PPAR alpha agonists will be delivered intravitreally by some other route (e.g., drug eluding pellet).

>>We have added a sentence to the relevant paragraph to temper our predictions, as recommended. It reads:
Whether the combination of fenofibrate and anti-VEGF agents will be viable for co-administration would need to be examined.

2. The authors should make the distinction between anti-VEGF agents improving diabetic macular edema and neovascularization, and systemic PPAR alpha agents slowing progression of retinopathy and thus decreasing risk of edema or neovascularization.

>> We have changed the wording in the relevant paragraph to clearly indicate that anti-VEGF therapies are used to treat diabetic macular oedema. Throughout the article, we have quite clearly indicated the role of fenofibrate.

Rafael Simó’s review:
1. In the first paragraph at the end of the sentence “Further, there is evidence from smaller studies of a potential benefit of thiazolidinediones (TZDs) on slowing the progression of DR in type 2 diabetes” appropriate references should be included.

>> We have edited the sentence and included the appropriate reference as follows:
A related class of compounds, the thiazolidinediones (TZDs), have been found to reduce progression to DR in at least one clinical trial [Shen et al., 2008].

2. The following sentence “Thus far, the beneficial effects of these agonists....” is ambiguous. What type of agonists are the authors referring to? Please check this sentence.

>>We have changed the sentence to read:
Thus far, the beneficial effect of PPAR agonists on the retinal vasculature has been observed following systemic delivery for the treatment of diabetic patients.
3. The authors use a lot of general references to PPARs. I recommend they reduce the number of these types of references and add the recent comprehensive review by Ciudin et al (Current Curr Top Med Chem. 2012;12:585-604).

>> We have now referred to this comprehensive review at relevant points in our paper and have removed a few older review articles that covered the same material. We are otherwise happy with our selection of references; where possible, we have used original, primary scientific papers on PPARs rather than reviews.

4. The mechanistic actions of fenofibrate at retinal level should be completed by adding a brief comment on the following essential references:


>>We read the above-mentioned papers and have commented on their findings in the relevant paragraph. It now reads:

Diabetic retinopathy is characterised by microangiopathy, which is thought to be caused by oxidative stress, advanced glycation end-products (AGEs), inflammatory mediators and endothelial cell death [44, 45, 46]. The beneficial effects of fenofibrate observed in the FIELD and ACCORD Eye studies could be due to reduced oxidative stress and inflammation, as well as effects on vascular function. Several studies have analysed the pharmacological mechanisms of fenofibrate individually. For example, fenofibrate has been shown to reduce circulating markers of oxidative stress in dyslipidaemic patients [47]. It has also been found to prevent inflammation by blocking AGE-induced NF-κB activation in animal models [48]. Fenofibrate has been found to ameliorate vascular function, improving blood flow in diabetics [49]. One recent study investigated the combined effects of fenofibrate on oxidative stress, inflammation and vascular tone in an animal model of diabetes [50]. This study found that fenofibrate improved vascular relaxation and increased expression of the antioxidant enzymes, superoxide dismutase and catalase [50]. Interestingly, they also observed a
decrease in the level of a proinflammatory marker, myeloperoxidase (MPO) [50]. Importantly, a comprehensive screen of donated human retinal pigment epithelia (RPE) revealed that PPAR\(\alpha\) (the receptor for fenofibrate) was highly expressed while PPAR\(\gamma\) was absent from the RPE [51]. Further, laboratory studies using human RPE cells under hyperglycaemic conditions found that fenofibrate reduced RPE monolayer permeability [52] via blocking activation of AMP-activated protein kinase (AMPK) [53, 54] and the reduction in permeability was dose-dependent, indicating that intraocular delivery of fenofibrate could be highly efficacious. In summary, there is an expanding molecular basis for the positive effect of fenofibrates observed in the FIELD and ACCORD eye studies.

Yours sincerely,

Maxwell Treacy and Tara Hurst