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COMMENT

# Cochrane corner: why we still don't know whether anti-TNF biologic therapies impact uveitic macular oedema

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In this Cochrane Corner commentary article, we considered the findings of the recent Cochrane systematic review by Robert Barry and colleagues on, "Anti-tumour necrosis factor biological therapies for the treatment of uveitic macular oedema (UMO) for non-infectious uveitis". The review reported that whilst the VISUAL I and VISUAL II randomised controlled trials both demonstrated that, in comparison to placebo subcutaneous injection, adalimumab significantly reduced the time to uveitis flare in patients whose intermediate, posterior, or pan uveitis had first been brought under control by oral steroid therapy, neither trial reported data on UMO. We discuss the meaning of composite clinical trial endpoints, and summarise key discussion points from the recent March 2019 American Uveitis Society workshop with international uveitis specialists, and representatives from the pharmaceutical and imaging industries, and the Food and Drug Administration (FDA) on, "Objective Measures of Intraocular Inflammation for Use in Clinical Trials". We explain why UMO is not currently considered to be an acceptable trial endpoint for drug licensing purposes. Finally, we return to the patient perspective and identify research priorities that would help to advance the field, and future updates of this Cochrane Review.

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Last month a 54-year-old woman with over 1000 µ of recurrent uveitic macular oedema (UMO) in her only-seeing eye presented to the uveitis clinic. The central vision in her other eye had been lost to a full-thickness macular hole, the fovea having succumbed to the chronic effects of waxing and waning UMO. As I turned to the electronic patient record with thoughts of a second-line agent, my heart sank to find that she had already tried both methotrexate and mycofenolate mofetil (antimetabolite immunosuppressants), and had developed a rash on adalimumab (a human monoclonal anti-TNF antibody). She had also since tried certolizumab-pegol (a monoclonal anti-TNF-α antibody fragment), which was ineffective for her joint inflammation, and was currently on secukinumab (a human monoclonal antibody targeting interlukin-17A). Fortunately, the UMO reduced to 400 µ after a week of high dose oral prednisolone followed by an Ozurdex implant, and since her psoriatic joints were actively inflamed again, she was able to switch to funded infliximab (a chimeric monoclonal anti-TNF-α antibody). But, I wondered, will this third anti-TNF agent reduce the severity or duration of UMO, or the risk of UMO relapse?

To find out, I turned to the recent Cochrane systematic review by Robert Barry and colleagues on, "Anti-tumour necrosis factor biological therapies for the treatment of uveitic macular oedema (UMO) for non-infectious uveitis" [1].

Uveitis is a leading cause of vision loss, estimated to cause between 10 and 25% of all blindness in high and low-middle income countries, respectively [2–5]. UMO accounts for 41% of vision impairment and 29% blindness in uveitis [6, 7]. We have numerous, effective off-license immunosuppressive drugs, but these have major side effects, both acutely and over the long haul [8].

One of the many new biologic therapies, adalimumab, was approved by NICE in October 2017 for patients in England who fail to respond, or are unable to tolerate, second line immunosuppressive therapy for sight-threatening active, non-infectious uveitis [9]. This funding

approval followed the publication of two important randomised controlled trials (RCTs). VISUAL I and VISUAL II both demonstrated that, in comparison to placebo subcutaneous injection, adalimumab significantly reduced the time to uveitis flare in patients whose intermediate, posterior or pan uveitis had first been brought under control by oral steroid therapy [10, 11].

Disappointingly, for such an important clinical question, the Jury is out. After searching the published and grey (unpublished) literature systematically, and screening 342 papers, Barry et al. identified no RCTs meeting the inclusion criteria. Whilst both VISUAL I and II included optical coherence tomography (OCT), data on UMO has not been published or reported.

In these two RCTs, excluded from the Cochrane Review, composite endpoints were used to define uveitis flare. A composite endpoint is a set of pre-specified endpoints. If any one is observed then the participant is considered to have attained the endpoint, and exits the trial. Composite endpoints are chosen for statistical efficiency, and can be justified if no single primary outcome measure would be expected in all patients. Uveitis can cause a host of sight-threatening problems for the eye, aside from macular oedema, for example, vitritis, anterior chamber inflammation, chorioretinal lesions, retinal vasculitis and sequelae of inflammation and its treatment, including cataract and glaucoma. However, a limitation of composite trial endpoints is that it is often the least clinically meaningful one that is observed first. In VISUAL I and II, the most frequently observed endpoint was a two-step decrease in vitreous haze score, and UMO was not included. Why is this?

On March 22nd and 23rd 2019, the American Uveitis Society and international uveitis subspecialists, pharmaceutical and imaging industry representatives, and representatives of the Food and Drug Administration (FDA) participated in a workshop on, "Objective Measures of Intraocular Inflammation for Use in Clinical Trials", hosted by the University of California, Los Angeles. This built on groundwork from an earlier workshop [12]. Here, representatives from the FDA articulated the multiple issues currently precluding UMO from being an acceptable trial endpoint. Firstly, they argued, macular oedema is not a direct measure of inflammation, and may be multifactorial. Furthermore, UMO waxes and wanes without necessarily causing a permanent loss of vision function. A longitudinal study is needed to identify whether some threshold of severity, or duration of UMO, exists, beyond which irreversible impairment of vision function occurs. If structural change can be significantly associated with a functional outcome, and if UMO is then included as an outcome measure in two clinical trials, then the FDA and other agencies internationally would likely accept it as a valid endpoint for drug licensing purposes.

The review by Barry et al. included change in quality of life as a secondary outcome measure. Clinicians track objective measures of each eye's structure (e.g., central foveal thickness) and function (e.g., visual acuity), but these measures provide only proxy measures of the impact of inflammatory eye disease on how a patient functions and is impacted by their disease. There has been increased recognition of the importance of the patient voice in ophthalmology in recent years [13], but no patient reported outcome measures have been developed for use in uveitis [14]. In fact, the workshop outlined that, as far as the FDA are concerned, to date, no validated patient reported outcome measures meeting their requirements have been used in any ophthalmology trials supporting a new drug licensing application [15].

Although Cochrane Eyes and Vision does not usually prioritise undertaking systematic reviews that are anticipated to be "empty", this review illustrates the value of the empty systematic review in highlighting important gaps in knowledge. Firstly, this review draws attention to the paucity of RCTs on the efficacy and safety of anti-TNF agents, in comparison to sham, placebo, each other, and other immunomodulatory therapies. Secondly, this review highlights the need for longitudinal epidemiological data on the structural risk factors associated with poor visual prognosis in uveitis, in order for these structural changes, which include UMO but are not limited to it, to become acceptable clinical trial endpoints. Finally, this review provides timely reminder that we need better patient reported outcome measures in inflammatory eye disease.

## Compliance with ethical standards

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