Colour photographs for screening in neovascular age-related macular degeneration: are they necessary?

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Abstract

Aims To investigate whether optical coherence tomography (OCT) with associated infra-red images provide enough information to determine treatment decisions in the management of neovascular age-related macular degeneration (nAMD), or whether retinal colour photography is also necessary. **Methods** In all, 87 OCT scans of 82 eyes with nAMD undergoing monitoring post ranibizumab treatment were taken using the Zeiss Stratus (Carl Zeiss Meditec, Jena, Germany; $n = 87$) together with their corresponding infra-red images. Fundus colour photographs were also taken. These images were reviewed by an experienced assessor, and a ranibizumab treatment decision was made during a multidisciplinary team retinal image review meeting.

Results In all, 30 OCT scans (34.5%) showed intraretinal or subretinal oedema. A total of 24 colour photographs (19.5%) demonstrated retinal haemorrhage. Corresponding OCT infra-red images gave poor sensitivity in detecting haemorrhages (0.176). In 16.7% of decisions to treat, haemorrhage alone was the deciding factor. Signs of disease activity seen only on colour photography were the deciding factor in clinical decisions for 8% of scans assessed.

Conclusions The presence or increase of intra-retinal oedema is an important sign of activity triggering ranibizumab retreatment, but some eyes show signs of retinal haemorrhage without coexisting oedema. These haemorrhages are often only seen on either colour imaging or fundoscopy and are unclear or invisible on OCT scans and infra-red images. Therefore, although retinal colour photography creates additional expense, it is

indispensable for making informed retreatment decisions, if patients are monitored using retinal imaging alone.

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Introduction

Age-related macular degeneration (AMD) is the commonest cause of blindness in people over 50 years of age in the developed world.¹ Neovascular AMD (nAMD) is characterised by ingrowth of new vessels from the choroid into the retinal pigment epithelial layer and subretinal space, known as choroidal neovascularisation (CNV). These fragile vessels can bleed, leading to scarring and loss of central vision. The resulting profound visual loss in a significant number of the ageing population exerts a heavy burden on healthcare resources.

The introduction of vascular endothelial growth factor (VEGF) inhibitors injected intravitreally has revolutionised the treatment of nAMD. The MARINA and ANCHOR trials demonstrated that 4-weekly injections of ranibizumab are an effective treatment for nAMD,^{2,3} leading to the United Kingdom licensing of the drug in February 2007 and UK NICE approval in 2008. Subsequently, the PRONTO study showed that OCT-guided Lucentis injections gave similar results to these other trials, but with fewer injections.⁴ On the basis of this small study, the United Kingdom has adopted a protocol of a loading regimen of three injections in the first instance spaced at

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4-weekly intervals, followed by 4 to 6 weekly monitoring to assess need for further injections.

The type of monitoring undertaken depends on the unit. In one clinic model, the patient may undergo retinal imaging using OCT together with fundoscopy review. Additional colour images may be taken. In the 'virtual clinic' model, the patient undergoes retinal imaging (OCT and colour imaging) but without fundoscopy. Occasionally fluorescein and/or indocyanine angiography may be carried out in either clinic model. Evidence that CNV is active is denoted by presence of oedema on OCT and/or haemorrhage on colour imaging or fundoscopy. In the PrONTO study, the main correlates assessed were the presence of subretinal fluid, retinal thickening, sight loss, or new haemorrhage. Further evidence for using lesion components for assessing nAMD activity has been provided by Hogg *et al*.⁵

Although costs are reduced by adhering to the PrONTO regime with decreased use of ranibizumab injections, this policy has meant that United Kingdom departments require robust and efficient imaging with subsequent accurate image interpretation. This is a time consuming and expensive process.

The basic nAMD surveillance protocol uses several imaging modalities to assess these correlates of disease activity. Oedema and retinal pigment epithelium detachment are best assessed by OCT for both classic and occult nAMD.⁶ OCT machines also provide an infra-red image, which may reveal a haemorrhage. Colour photography of the retina is carried out, particularly in the virtual clinic context where fundoscopy is not used, so that images of the fundus are available to document haemorrhages and other pathological correlates of nAMD.⁷ The need for both screening modalities increases the time and cost of monitoring nAMD patients, as the colour fundus camera is usually a 'stand alone' camera and may be in a different room from the OCT machine, necessitating transfer of the patient from one room to another to obtain both types of imaging.

This study considered whether the use of Zeiss OCT infra-red images alone was sufficient for detecting haemorrhages (denoting nAMD activity), or whether the use of colour photography was necessary to detect haemorrhage. We also assessed the key factors leading to retreatment decisions in the study cohort to consider whether the use of colour photography led to a difference in the number of patients retreated.

Patients and methods

Patients

OCT scans and colour photographs from 73 patients were assessed in the retinal image review clinics at the

Oxford Eye Hospital over a period of 7 weeks. Although each patient had both eyes evaluated, only eyes that were under treatment were included in the study. In all, 5 of the 73 patients were assessed twice in the 7-week interval and 9 had both eyes included in the study, leading to the assessment of 87 scans in total. Each of these patients had a diagnosis of nAMD and a history of treatment with ranibizumab.

Image acquisition

OCT imaging was performed using Stratus OCT III (Carl Zeiss Meditec). In all, 87 scans were acquired using Stratus OCT. Retinal colour photographs were taken during the same session as corresponding OCT scans using the Zeiss FF450 + fundus camera.

Assessment

Single line OCT scans, infra-red images, and retinal colour photographs were assessed by the medical retinal specialist (SD) for correlates of active CNV. The appropriate line scan is preselected by the photographer. For the purposes of this study, that pre-selected one line image was reviewed with its associated infra-red image, followed by an assessment of the associated colour photograph. Although in the 'virtual clinic', the previous infra-red images would be available for comparison; in this study we only used the most recent infra-red image.

The observer was asked to comment on images provided by all three modalities for each eye assessed. Factors assessed were the presence or absence of oedema on OCT, the presence or absence of haemorrhage or scarring on infra-red image and finally the presence or absence of haemorrhage, pigment or other nAMD features on retinal colour photography.

A clinical decision to treat or not treat was made by the medical retinal specialist based on the findings from the OCT scan and colour photography in addition to visual acuity. The reason behind each decision to treat was discussed and recorded.

Results

Oedema

A total of 30 out of 87 scans (34.5%) were judged to show oedema on the basis of OCT scans. Infra-red images and colour photography had no role in the assessment of oedema.

Haemorrhage

Retinal colour photography demonstrated the presence of haemorrhage in 17 of the photographs (19.5%), which was

missed in 82% of corresponding infra-red images. Table 1 illustrates the number of haemorrhages detected by infra-red and colour photography in the study. Compared with the haemorrhages detected by colour photography, the sensitivity and specificity of Stratus infra-red images was 0.176 and 0.971, respectively. Figure 1a shows a retinal colour photograph indicating a haemorrhage. Figure 1b shows the associated ambiguous Stratus infra-red image.

Other nAMD features

Other features of nAMD observable on colour photography were not distinguishable on infra-red images. These include drusen, pigment, disciform, and atrophic changes. The only other feature noted in the infra-red image analysis in addition to haemorrhages was scarring.

Decision to treat

Review of 87 retinal images led to 30 decisions to treat with a further ranibizumab injection and 57 decisions not to treat. Of the 30 decisions to treat, 19 were made on the basis of oedema on the OCT scan alone (63.3%), 5 were made on the basis of haemorrhage seen on colour photography alone, in which oedema had not been detected on OCT (16.7%) and 9 were made on the basis of both oedema and haemorrhage (20%).

Table 1 Sensitivity and specificity for detection of retinal haemorrhages using infra-red imaging

Total scans	87
Total number of haemorrhages observed on colour photographs	17
Haemorrhages visible on infra-red image	3
Haemorrhages incorrectly queried on infra-red image	2
Sensitivity (95% CI)	0.176 (0.047–0.442)
Specificity (95% CI)	0.971 (0.891–0.995)

Of the five patients who were treated on the basis of haemorrhage alone, only one of these haemorrhages was observed on the infra-red images supplied by the OCT scanner. In two other scans, the colour photography revealed significant fibrosis, so that despite oedema observed on OCT scan, it was decided that the macular degeneration was too advanced for treatment to be effective, leading to a decision not to treat.

Overall, information provided by colour photography that was not observable on other imaging modalities directly influenced the clinical decision whether to re-treat in 8% of the patient cohort.

Discussion

Access to good quality imaging to determine need for retreatment is vital in the ongoing management of nAMD based on repeated frequent anti-VEGF injections. The purpose of this study was to determine whether the combination of OCT with associated infra-red images is sufficient to inform decisions of ranibizumab retreatment, or whether retinal colour photographs are also needed. Specifically, the question of whether infra-red images could replace colour photography in the detection of haemorrhages, and whether haemorrhage detection was an important factor in retreatment decisions was addressed.

Our results reviewing the Stratus infra-red images showed that infra-red images are unreliable for the detection of retinal haemorrhages. These infra-red images failed to pick up other correlates of nAMD activity which can indicate that disease has progressed beyond the treatable stage. Our results suggest that an infra-red image is not adequate in nAMD surveillance without fundus review or colour imaging.

In this study, the presence of oedema (observed on OCT scan) was the most important trigger for ranibizumab retreatment, with 83.3% of the patients

Figure 1 (a) Colour image showing large haemorrhage and (b) corresponding Stratus infra-red image provides no useful information.

treated exhibiting oedema on OCT scan. However, 36.7% of patients deemed to require retreatment had haemorrhages, and in 16.7% of the treated cohort this was the key feature leading to retreatment. Therefore, in this cohort the additional information provided by colour photography was significant for the clinical decision made regarding treatment, with 8% of clinical decisions made on the basis of information supplied by colour photography alone. nAMD surveillance made on the basis of OCT scans and infra-red images alone would be likely to undertreat in cases where haemorrhage, but no oedema, is present.

It is important that all line scans are reviewed rather than just using a single line OCT scan to make sure that the presence of oedema is identified. In cases in which infra-red imaging is of high enough quality that a haemorrhage is suspected, it is helpful to review previous images to ascertain whether the haemorrhage is new. Our study has shown that, while using Stratus infra-red imaging, it is still necessary to have either a colour image or funduscopy. However, it is also important to note that colour imaging can be difficult to interpret as differing levels of exposure can render pigment similar in appearance to haemorrhage and vice versa. In these instances, fundus examination, fundus fluorescein angiography, and/or indocyanine green angiography can be extremely helpful in confirming or excluding a haemorrhage due to nAMD.

This study did not directly assess the importance of visual deterioration in decisions for further treatment. Although deterioration may be a sign of active nAMD, it may also occur in the context of fibrosis and therefore be an unreliable indicator of nAMD activity. As well as monitoring the response to treatment, intra-ocular pressure should also be kept under surveillance.

The use of OCT-guided ranibizumab retreatment has placed huge demands on imaging services, and therefore the simplest methods of surveillance should be sought. However, this study has shown that OCT imaging alone is not enough to determine nAMD activity. As a fresh haemorrhage is assumed to be evidence of disease activity, colour photography, or funduscopy remain necessary in nAMD monitoring. New combined imaging modalities may improve the surveillance of nAMD and ranibizumab retreatment decisions, but the current best practice is the combination of OCT and retinal colour photography or funduscopy.

Summary

What was known before

- There is little in the literature regarding what retinal imaging is best suited for the ongoing management of exudative age-related macular degeneration (AMD). Optical coherence tomography has been described in assessing AMD but no formal study has been carried out to assess its efficacy as a sole imaging device in picking up active exudative AMD.

What this study adds

- Our study has shown that optical coherence tomography alone is not able to identify all patients who require treatment, and recommends that colour imaging and/or funduscopy is also required.

Conflict of interest

The authors declare no conflict of interest.

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