EDITORIAL

Action on sickle cell retinopathy: the time is now

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Despite sickle-cell disease being one of the commonest genetic disorders in the UK, with ~14,000 people affected [1], there is no clear guidance on sickle cell retinopathy screening or treatment and no clear picture of the current natural history and prevalence of retinopathy in the UK. Progress has been slow in developing effective systemic treatments with, until recently, hydroxycarbamide (hydroxyurea) being the only drug approved to treat sickle cell disease in the United Kingdom.

However, 3 new drugs have been approved by the US Food and Drug Administration [2] and one of these, crizanlizumab, has just been approved by NICE, heralding new hope for this much neglected disease [3]. In parallel, recent advances in ocular imaging, present a unique opportunity for the ophthalmic community to contribute to closing the knowledge gap that still exists in our understanding and management of sickle cell retinopathy and sickle cell disease.

Classified by Goldberg in 1971 [4], sickle cell retinopathy remains one of the most recognisable systemic disease associations in the field of retina. Natural history data largely comes from cohort studies from Jamaica in the 80s and 90s noting the higher prevalence of proliferative sickle retinopathy in people with SC genotype and a high incidence of spontaneous regression [5–7]. However, does this apply now? UK patients may be more genetically diverse, compared to those in Jamaica, and the treatment of sickle cell disease has changed since these early studies were conducted. Babies born in the UK are now screened for the sickle cell gene [8] and are actively managed, including starting hydroxycarbamide, which has greatly improved life expectancy and hopefully will improve on the previously reported natural history [9]. However, increasing age is an established risk factor for proliferative sickle retinopathy [5] and we may still see higher prevalence of advanced sickle retinopathy as the population ages. In addition, increased migration is bringing patients to the UK at different stages of the disease, some of whom may not already have a diagnosis of sickle cell disease on presentation.

Whilst proliferative sickle retinopathy can regress, we do not yet understand the factors that promote regression [5]. There is evidence from two randomised controlled trials conducted over 30 years ago that scatter laser photocoagulation leads to a modest reduction in the occurrence of vitreous haemorrhage and visual loss in eyes with proliferative retinopathy compared to observation but which laser technique and when to intervene remains uncertain [10]. Although the incidence of visual impairment due to sickle retinopathy has not been published in UK, case series from units in the UK serving populations with a high prevalence of sickle cell disease reflect ongoing occurrence of significant irreversible visual impairment following vitrectomy for eyes that progress to vitreous haemorrhage and retinal detachment (stage 4 and 5 proliferative sickle retinopathy) [11, 12]. Anti-VEGF injections are being used by some clinicians to control neovascularisation [13]. Further trials on when to intervene and how are needed.

Studies have shown that ultra-widefield fundus photography (UWF-FP) more reliably detects sickle cell retinopathy than clinical examination or standard field fundus photography in adults and paediatric populations [14, 15]. Visual loss can also occur due to maculopathy, which was not included in the earlier disease classifications.

Optical coherence tomography (OCT) and OCT-angiography (OCT-A) imaging enable us to non-invasively observe the impact of sickle cell disease on the macular structure and vasculature. Studies have shown us that the prevalence of sickle maculopathy is much higher and occurs earlier than previously described [16]. Multiple structural OCT changes have been described in sickle maculopathy such as foveal splaying, inner and outer retinal thinning predominantly in the temporal region of the macular and choroidal thinning [17]. Fluorescein angiography (FA) remains the gold standard for staging and monitoring sickle cell retinopathy, with UWF-FA enabling visualisation of vascular features and leakage of sickle retinopathy lesions in the far periphery [18]. Positive correlations between macular thinning on OCT and ischaemic index on UWF-FA have been reported, suggesting a possible role for macular OCT in screening for proliferative sickle retinopathy [19]. OCT-A quantitative metrics have been demonstrated to precede macular thinning, supporting the hypothesis that thinning is as a result of accumulation of vaso-occlusive events at the level of the retinal capillaries [20]. Wide-field swept OCT-A may help advance its value.

There are no prospective studies evaluating the impact of current systemic treatments on the evolution of proliferative sickle retinopathy although it is logical to deduce systemic therapy that reduces vaso-occlusive events will positively impact on incidence and progression of sickle retinopathy. For instance, red cell exchange transfusion has been shown to stabilise rapidly progressive proliferative sickle retinopathy in a case report [21]. Hydroxycarbamide increases the production of HbF (HbF does not sickle) and in one retrospective case series, children with HbF <15% had a 7.1-fold higher odds of developing sickle retinopathy [22]. Mian et al. reported similarly positive effects of HbF levels over 15% in a retrospective cross-sectional study of 300 adults with HbSS [23]. Hydroxycarbamide therapy has also been shown to be associated with reduced rates of retinal thinning on OCT [24].

We believe national sickle cell retinopathy screening guidelines mandating annual screening from age of 10 years with UWF-FP and OCT need to be considered. An associated, funded image database hub linked to the national haemoglobinopathy registry, would provide researchers with invaluable data to continue to unravel the evolution of sickle retinopathy, the influence of systemic parameters and therapies on progression of sickle cell retinopathy, as well as allowing researchers to understand whether ocular imaging parameters can predict systemic progression and complications reliably and be used to help guide haematologists in their use of the additional new treatments as they become available. Such progress is long overdue and much deserved.

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Christiana Dinah ¹✉, Brigit Greystoke², Isabella Mueller ² and James Talks²
¹London North West University Healthcare NHS Trust, Watford Road, Harrow, HA1 3UJ London, UK. ²Royal Victoria Infirmary, Newcastle Hospitals NHS Foundation Trust¹, Newcastle Upon Tyne, UK.
 ✉email: christiana.dinah@nhs.net

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AUTHOR CONTRIBUTIONS

CD conceived the work, drafted and revised the work and approved final version, BG contributed to draft, revised the work and approved final version, IM contributed to draft, revision and approved final version and JT conceived the work, contributed to draft and revised the work and approved the final version.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Christiana Dinah.

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