The ROYAL COLLEGE of OPHTHALMOLOGISTS

BRIEF COMMUNICATION

Revisiting NICE guidelines for initiation of intravitreal anti-VEGF therapy for centre-involving diabetic macular oedema: a survey of current interpretation in the United Kingdom

Christiana Dinah[1✉], Sam Myers[1], Sreekumari Pushpoth[2] and Simona Degli-Esposti[3,4]

Eye (2022) 36:1832–1834; https://doi.org/10.1038/s41433-022-01935-5

The National Institute of Health and Care Excellence (NICE) in England and Wales, (adopted in Northern Ireland) recommends intravitreal aflibercept (TA 346) or ranibizumab (TA 274) as first-line treatment options for patients with visual impairment due to centre-involving diabetic macular oedema (CI-DMO) and a central retinal thickness (CRT) of ≥ 400 µm on optical coherence tomography (OCT) [1, 2].

Anecdotal evidence suggests that interpretation of "CRT" and "visual impairment" as described within NICE guidelines varies across the UK. This may result in variable access to treatment for patients with CI-DMO. In addition, in DMO, the CRT does not always correlate well with visual impairment [3], with some patients in clinical practice presenting with good VA despite significant CI-DMO.

In April 2021, a 6-item online questionnaire-based survey was sent to medical retina specialists in England, Wales and Northern Ireland to understand how the NICE guidelines for intravitreal anti-VEGF treatments for CI-DMO are interpreted when initiating treatment. Ethical approval of this survey was waived by the research and development department at London North West University Healthcare NHS Trust as no medical assessment/intervention was performed and all participants are medical professionals. Appendix 1

Of all 102 respondents, 94 were medical retina specialists who currently manage patients with DMO in England, Wales and Northern Ireland.

There was a clear lack of consensus, with 38 of the included respondents (40.4%) initiating treatment when the central 1 mm ETDRS subfield value ≥400 µm, 32 respondents (34%) initiating when any point within the central 1 mm ETDRS subfield of the macula is ≥400 µm and a further 23 respondents (24.5%)

initiating treatment when any ETDRS subfield within the central 3 mm centred on the fovea is ≥400 µm. One respondent said they would use any of the definitions to enable access to treatment if there was visual impairment. Figure 1 illustrates these interpretations of CRT and Fig. 2 illustrates variability of visual acuity criteria for initiating intravitreal anti-VEGF therapy for CI-DMO.

A majority of respondents (57 respondents, 60.6%) said they would treat a patient with VA ≥ 6/7.5 Snellen (LogMAR 0.1 or 79 ETDRS letters) associated with CRT of ≥400 µm. The main drivers for the decision to treat were: the patient complaining of visual impairment (44 respondents, 72%), the CRT meeting NICE guidelines (41 respondents, 71.9%), the presence of poor vision in the fellow eye (36 respondents, 63.2%), presence of proliferative diabetic retinopathy (PDR) in the affected eye (28 respondents, 49.1%), and poor control of diabetes or other complications of diabetes (25 respondents, 43.9%).

Of those who opted not to treat such a patient (37 respondents), 29 (73.2%) cited the evidence from the DRCR.net's Protocol V study as their reason for not treating and 22 (59.5%) said they felt the risks of treatment outweighed the benefits in patients with good VA. The most common follow up interval for observation was 3-monthly (25 respondents, 67.6%).

There is significant variability in the interpretation of CRT and the use of visual acuity threshold for the initiation of intravitreal anti-VEGF treatment for CI-DMO in the UK. Such variation may result in unequal access to treatment across the UK and potentially exacerbate health inequalities. Including subfield 1–5 in the definition of CRT allows clinicians to avoid applying laser therapy to areas relatively close to the fovea reducing potential increased risk of scotoma or foveal burn. Alternative interpretations of CRT may also allow clinicians to treat patients with visual impairment but CRT < 400 µm, thereby widening access to treatment.

The inclusion of a CRT threshold in these NICE guidelines is fraught with difficulty. Whilst eyes with CRT ≥ 400 µm demonstrated greater relative efficacy and therefore cost- effectiveness in the registration trials presented to NICE, there are well described sex and race-related differences in normal CRT and foveal morphology. CRT in women is, on average, up to 15 µm thinner than men [4]. People of African and Afro-Carribean descent have also been demonstrated to have CRT of up to 30 µm thinner than Caucasian counterparts [4, 5]. Thus, a simple CRT treatment-initiation threshold of ≥400 µm may inadvertently result in women and people of African and Afro-Carribean descent requiring higher volumes of fluid for initiation of intravitreal anti-VEGF therapies for DMO since they are starting from a lower normal CRT. This is

[1]Department of Ophthalmology, London North West University Healthcare NHS Foundation Trust, London, UK. [2]Department of Ophthalmology, James Cook University Hospital, Middlesbrough, UK. [3]Medical Retina Department, Moorfields Eye Hospital NHS Foundation Trust, London, UK. [4]NIHR Biomedical Research Centre at Moorfields Eye Hospital and UCL Institute of Ophthalmology, London, UK. ✉email: christiana.dinah@nhs.net

Received: 20 September 2021 Revised: 9 January 2022 Accepted: 12 January 2022
Published online: 25 January 2022

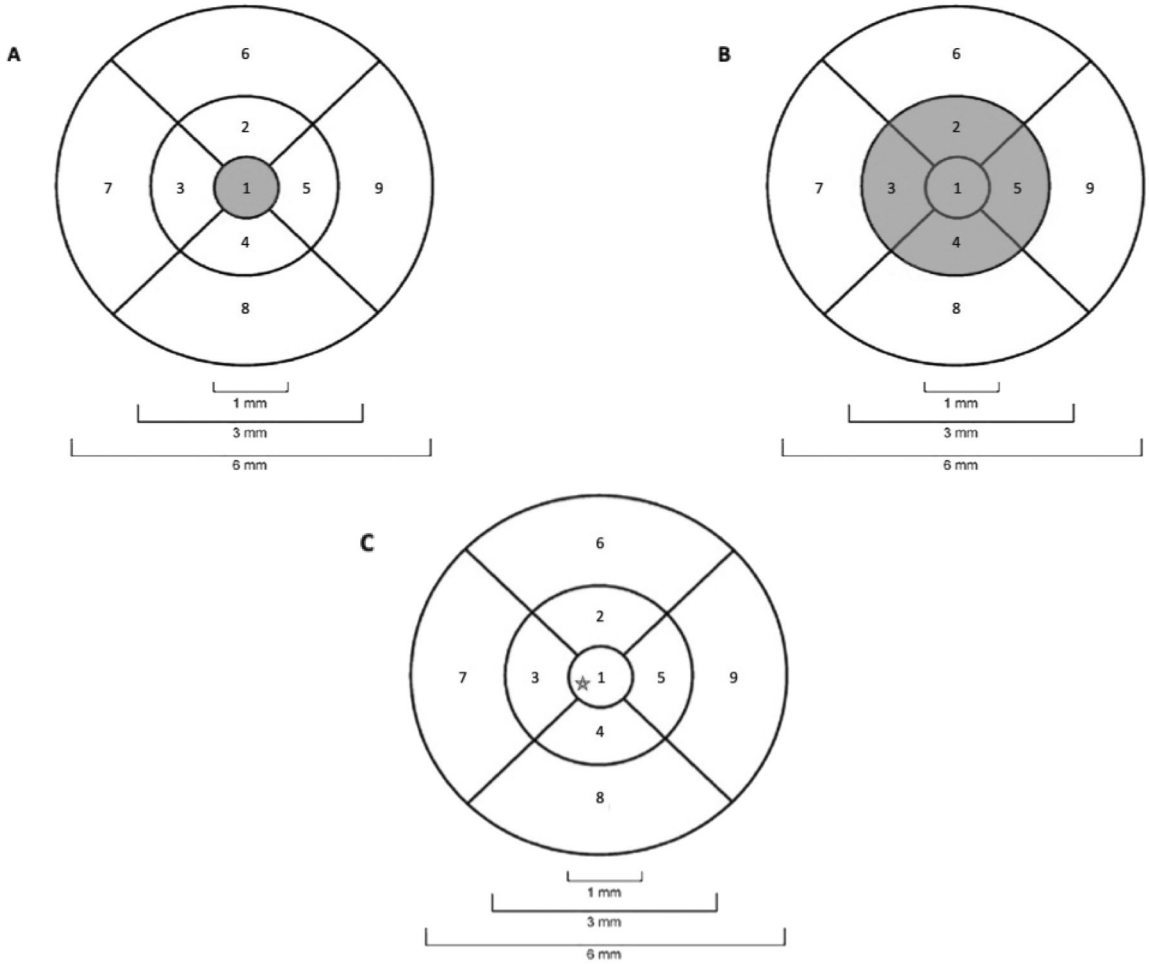

Fig. 1 Interpretation of 'CRT' for initiation of anti-VEGF therapy for CI-DMO by medical retina specialists. A CRT ≥ 400 µm defined as the mean value of all thickness values obtained in the central 1 mm subfield meeting this threshold. **B** CRT ≥ 400 µm defined as the mean value of all thickness values obtained in the central 1 mm subfield or any of subfield 2–5 meeting this threshold. **C** CRT ≥ 400 µm defined as any single point within the central 1 mm subfield meeting this threshold on the thickness profile.

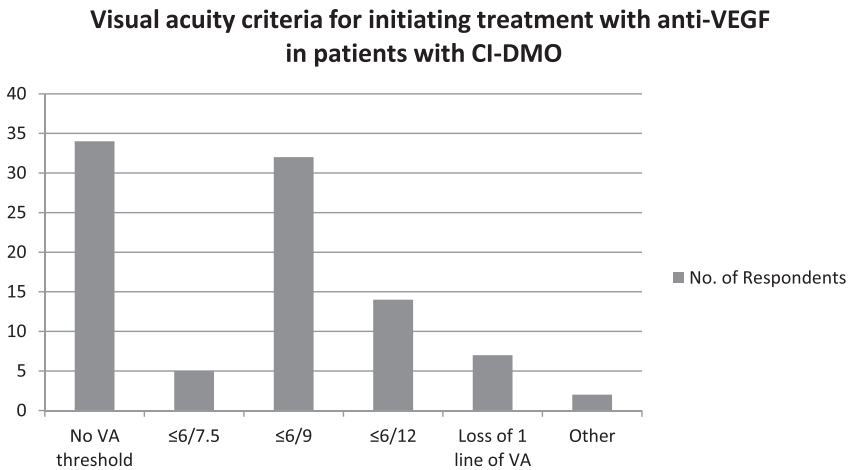

Fig. 2 Visual acuity criteria used by medical retina specialists for initiating anti-VEGF therapy for CI-DMO. Illustrates the variability in incorporation of visual acuity (VA) criteria when initiating intravitreal anti-VEGF for CI-DMO.

supported by a recent UK study reporting that time-to-treatment for diabetic eye disease once referred into a hospital clinic, is longer for patients of African descent than their Caucasian or South Asian counterparts [6].

We assert that "central retinal thickness" needs to be defined more specifically within the guidelines to ensure equity of access to anti-VEGF therapy across the National Health Service in the UK. We further propose CRT should be adjusted for sex and ethnicity

to ensure equity of access. Well-designed, inclusive studies are required to determine the optimal management strategy for patients with CI-DMO, good VA and high CRT.

REFERENCES

1. Overview | Aflibercept for treating diabetic macular oedema | Guidance | NICE. https://www.nice.org.uk/guidance/ta346 (accessed Aug 2021).
2. Overview | Ranibizumab for treating diabetic macular oedema | Guidance | NICE. https://www.nice.org.uk/guidance/ta274 (accessed Aug 2021).
3. Diabetic Retinopathy Clinical Research Network, Browning DJ, Glassman AR, Aiello LP, Beck RW, Brown DM, Fong DS, et al. Relationship between optical coherence tomography-measured central retinal thickness and visual acuity in diabetic macular edema. Ophthalmology. 2007;114:525–36. https://doi.org/10.1016/j.ophtha.2006.06.052.
4. Kelty PJ, Payne JF, Trivedi RH, Kelty J, Bowie EM, Burger BM. Macular thickness assessment in healthy eyes based on ethnicity using Stratus OCT optical coherence tomography. Invest Ophthalmol Vis Sci. 2008;49:2668–72. https://doi.org/10.1167/iovs.07-1000.
5. Ctori I, Huntjens B. The association between foveal morphology and macular pigment spatial distribution: an ethnicity study. PloS ONE. 2017;12:e0169520. https://doi.org/10.1371/journal.pone.0169520.
6. Kirthu V, Reed KI, Gunawardena R, Alattar K, Bunce C, Jackson TL. Do Black and Asian individuals wait longer for treatment? A survival analysis investigating the effect of ethnicity on time-to-clinic and time-to-treatment for diabetic eye disease. Diabetologia. 2021;64:749–57. https://doi.org/10.1007/s00125-020-05364-5.

ACKNOWLEDGEMENTS

Christine Kiire for assistance preparing the manuscript.

AUTHOR CONTRIBUTIONS

CD contributed to study design, data extraction, analysis and manuscript writing, preparation and revision. SM contributed to study design, data extraction, analysis, and manuscript preparation and revision. SD contributed to study design, analysis, manuscript preparation and revision, SP contributed to study design, analysis, manuscript preparation and revision, CD is the guarantor of the work.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41433-022-01935-5.

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

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.