Belfast briefing: Retina Day roundup from the RCOphth 2024 Annual Congress

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Belfast hosted this year's Royal College of Ophthalmologists' (RCOphth) Annual Congress, a meeting dedicated to sharing advances, knowledge and clinical practice points in ophthalmic care. This article summarises selected talks by medical and surgical retina specialists during the Retina Subspecialty Day.

An insider's update on NICE guidance for diabetic retinopathy

Christiana Dinah (London Northwest University Healthcare NHS Trust), a member of the advisory diabetic retinopathy (DR) guideline committee, presented an update on draft National Institute for Health cand Care Excellence (NICE) guidance for DR (Table 1), final publication expected soon [1]. This guidance would be applicable to all settings where NHS-funded care is provided, including independent sector treatment centres. In NICE speak, the term 'offer' relates to a strong recommendation where there is clear evidence of benefit; 'consider' relates to actions where evidence is less certain.

Refer or follow up for epiretinal membrane / lamellar hole surgery?

Arijit Mitra (Sandwell and West Birmingham NHS Trust) outlined evidence-based recommendations from a RCOphth Concise Practice Point on the management of patients with idiopathic epiretinal membrane (ERM) [2]. Most ERM is idiopathic, although common secondary causes include cataract surgery, retinal vascular disease, uveitis and retinal tears [3].

Idiopathic ERM may be classified as symptomatic (worsening of vision, distortion of vision, loss of depth perception) or asymptomatic. Referral to hospital eye vitreoretinal services is advised if there is decrease in distance vision (to 6/12 or loss of two lines from baseline and no other reason for decreased vision) and / or presence of either metamorphopsia, aniseikonia, decreased binocular function, reading speed and lifestyle changes due to decreased visual acuity. Practitioners should beware of ocular dominance, which sometimes can mask symptoms. If the decision by the vitreoretinal team is not to operate, the patient may be referred back to the optician for yearly follow-up, with re-referral if necessary. Asymptomatic patients with good visual acuity can be monitored in the community by an optometrist.

Overall, 10–30% of patients that present to surgeons and are initially observed progress to surgery within a 2–7-year period. Patients with good vision (≥6/12) and asymptomatic are less likely to progress rapidly or require surgery. Those who are symptomatic with inner and outer retinal changes are more likely to progress and require surgery. Internal limiting membrane (ILM) peel can be performed in addition to the ERM peel and has been shown to reduce the recurrence rate of ERMs. However, there is no evidence that ILM peeling improves final visual acuity or reduces metamorphopsia as compared with pars plana vitrectomy plus ERM peel only. Mitra emphasised the need for a systematic approach and to manage expectations in the treatment of ERM.

Is imaging the vitreous useful?

Professor Paulo-Eduardo Stanga (The Retina Clinic London) highlighted the role of imaging the vitreous: to objectively assess posterior vitreous detachment (PVD) status; to confirm or rule out vitreous attachments and traction; and to assess symptomatic vitreous floaters and opacities (VFO). Prof Stanga also discussed the role of ultra-widefield imaging and indirect ophthalmoscopy with 360-degree scleral indentation, and emphasised that the latter examination modality is essential in order to examine the peripheral retina and rule out rhegmatogenous lesions, as it is the only way to examine the retina up to the ora serrata and therefore perform a pan-retinal examination.

A large, community-based prospective study found a 9.9% rate of retinal tears or rhegmatogenous retinal detachment at the time of PVD, underscoring the importance of indentation indirect ophthalmoscopy [4]. Preexisting asymptomatic vitreous floaters usually become symptomatic after PVD.

Table 1: Summary highlights of draft NICE guidance on diabetic retinopathy [1].

Systemic management in DR
- When initiating a diabetes treatment that is likely to result in a rapid, substantial drop in the person's HbA1c, notify the person's ophthalmologist so the person can have an early review.
- Consider fibrates for people with non-proliferative retinopathy and type 2 diabetes to reduce the progression of DR.

Cataract surgery
- Before undertaking cataract surgery for a person with diabetes, the surgeon should obtain information about the person's current diabetic eye disease status. This can be used by the surgeon to tailor the surgery to the person's eye condition, give correct postoperative medication, and tailor follow-up to the patient's needs.

Non-proliferative retinopathy
- Hospital eye services should monitor disease progression in people with moderate, severe or very severe non-proliferative retinopathy who are not being currently treated and have not been previously treated. Suggested review frequences are every 6–12 months for moderate non-proliferative DR and every 3–6 months for severe or very severe non-proliferative DR.

Proliferative DR
- Consider using ultra-widefield fundus imaging alongside clinical examination when assessing the eyes of patients for the presence of proliferative diabetic retinopathy (PDR).
- Offer panretinal photocoagulation (PRP) to all patients when they are first diagnosed with PDR.
- Start PRP within two weeks of offering it and complete it withing four weeks of starting treatment.
- Offer additional anti-VEGF treatment for people whose PDR remains active after complete PRP; if more than one anti-VEGF is available, use the cheapest.

Diabetic macula oedema (DMO)
- Offer macular laser treatment to people with non-centre-involving clinically significant macular oedema.
- When people have centre-involving DMO and good vision (79 letters or better) consider observation or macular laser. Discuss these two options with the person with macular oedema.
- When people have centre-involving DMO, central retinal thickness of <400 µm and visual impairment (78 ETDRS letters or worse, 6/9 or worse), consider anti-VEGF treatment or macular laser. If more than one anti-VEGF is available use the cheapest.
- If anti-VEGF alone does not stabilise or improve the person's vision after the loading phase, consider using macular laser as rescue treatment or changing anti-VEGF treatment.
- Suboptimal treatment response for DMO is defined as reduced vision due to DMO, increased DMO, or no change or increase in retinal thickness after the anti-VEGF loading dose.
- Assess response to treatments after 12 months; consider switching to dexamethasone intravitreal implant if the response is suboptimal.

Prof Stanga proposed a new diagnostic methodology (SK-VFO Test) for the assessment of VFO and understanding of their impact on vision [5]. He also stressed that treatment options are available for symptomatic PVD and vitreous floaters (e.g. full or limited vitrectomy, or Nd-YAG vitreolysis). He outlined the surgical procedure of selective vitrectomy for VFO, utilising 25- or 27-gauge vitrectomy instrumentation for VFO / core vitreous removal, with no intraoperative induction of PVD and no removal of posterior cortical vitreous, if attached, nor removal of anterior / retrolental nor peripheral vitreous. New anatomical and functional testing methodology is necessary to objectively assess effect of VFOs and personalise treatment [6]. Prof Stanga added that correlation between patients' subjective symptoms and imaging and functional test results enables the identification of best candidate patients for treatment.

New treatments for AMD

Advances in the retinal pipeline for age-related macular degeneration (AMD), reviewed by Professor Sobha Sivaprasad (Moorfields Eye Hospital), provide promising strategies across the AMD staging classification: intermediate AMD, to prevent or delay progression to advanced AMD; geographic atrophy (GA), to decrease rate of progression of GA growth and / or prevent progression of ellipsoid zone loss; and, for neovascular AMD, maintain sustained disease control, for example with novel long-acting delivery routes, bispecific antibody therapy, high dose anti-vascular endothelial growth factor (anti-VEGF), and investigational gene therapies.

What are reticular pseudodrusen and why do we care?

Multimodal imaging, particularly optical coherence tomography (OCT), has allowed a greater appreciation of reticular pseudodrusen (RPD) (also known as subretinal drusenoid deposits), their prevalence and their location above the retinal pigment epithelium (RPE), noted Professor Robyn Guymer (The Centre for Eye Research Australia, University of Melbourne). Prof Guymer explained that RPD in eyes with AMD is a phenotype that is more common than previously recognised [7]. Reticular pseudodrusen increase the risk of late AMD development particularly for GA. The LEAD trial, evaluating subthreshold nanosecond laser (SNL) intervention in AMD, suggested that the effect of a treatment in the early stages of AMD could differ based on the presence of RPD, underscoring the importance of recognising this phenotype, particularly as novel treatments to slow disease progression are being investigated [8]. Results showed a ~4-fold reduced progression rate for the 76% participants without RPD at baseline with SNL treatment, and a ~2.5-fold increased progression rate for the 24% participants with RPD with SNL treatment. Prof Guymer proposed a hypothesis informed by histological studies that RPE dysfunction and altered immune function are likely implicated in the pathogenesis of RPD.

Assessing and diagnosing retinal vasculitis

Retinal vasculitis, with or without occlusion, is a serious adverse event that can lead to vision loss and has previously been reported in patients treated with anti-VEGF agents and complement inhibitor therapy. Nicholas Beare (St Paul's Eye Unit, Liverpool University Hospitals NHS Foundation Trust) reviewed considerations in assessing and diagnosing retinal vasculitis. He highlighted research evaluating a novel grading scheme for retinal vasculitis utilising

Table 2: Summary profile of commonly used intravitreal VEGF inhibitors.

	Ranibizumab	Aflibercept 2mg	Aflibercept 8mg	Faricimab
MoA	VEGF-A inhibition	VEGF-A and PGF inhibition	VEGF-A and PGF inhibition	Dual VEGF-A/Ang-2 inhibition
nAMD/DMO initiation	1	3/5	3	4
Longest interval (weeks)	-	16	20	16
Minimal interval (weeks)	4	4	8	4
Injection volume (µL)	50	50	70	50
Inflammation	low	low	low	low

Abbreviations: Angiopoietin 2 (Ang-2); mechanism of action (MoA); neovascular age-related macular degeneration (nAMD); placental growth factor (PGF). Adapted from: Gale R. Which anti-VEGF should I use? RCOphth 2024 Annual Congress Retina Subspecialty Day. 20–3 May 2024; Belfast, UK.

widefield fluorescein angiography and the development of a deep learning model that could perform reliable segmentation for retinal vascular leakage and occlusion in fluorescein angiograms of patients with retinal vasculitis [9,10].

When is it TB?

Helen Devonport (Bradford Teaching Hospitals NHS Foundation Trust) provided a recap on basics of tuberculosis (TB) infection and outlined challenges in diagnosing ocular TB. Mycobacterium tuberculosis (Mtb) is the primary organism responsible for TB infection and disease and is spread by airborne particles from those with pulmonary or laryngeal TB. Ocular TB, defined as intraocular inflammation (uveitis) associated with presumed or proven TB infection, can affect any part of the eye. Typical phenotypes include peripheral occlusive retinal vasculitis, choroidal granulomas, and serpiginous or serpiginous-like chorioretinopathy [11]. A consensus BTS clinical statement recommends that, in all cases, ocular TB should be treated as active TB disease [11]. Patients with suspected ocular TB should be managed jointly by ophthalmic specialists and TB specialists [11].

Should we be offering red light therapy?

Ben Burton (James Paget University Hospitals NHS Foundation Trust) discussed multiwavelength photobiomodulation (PBM) therapy as a potential non-invasive treatment option for subjects with nonexudative AMD. Photobiomodulation involves light from the visible spectrum to near infrared (500–1000nm) applied to selected tissues to produce beneficial cellular effect [12]. Two-year data from the LIGHTSITE III trial demonstrated sustained vision improvement in nonexudative AMD subjects treated with PBM using the Valeda® Light Delivery System (LumiThera) [13]. Treatment was given in a series of nine sessions over 3–5 weeks, repeated every four months. Occurrence of new GA was observed in 24.0% of sham vs. 6.8% of PBM eyes. Photobiomodulation treatment showed a favourable safety profile with high compliance and no signs of phototoxicity. Study findings are interesting and further evaluations appear justified.

Who should we consider for current GA treatments?

Professor Usha Chakravarthy (Queens University of Belfast) reviewed current potential treatment approaches for GA. Geographic atrophy growth rate is greater when extrafoveal or multifocal [14]. Phase 3 clinical trials of complement pathway inhibitors show reduction in GA growth but no altered rate of vision loss. Prof Chakravarthy explained that change in function and expansion in GA area are not co-linear, with higher function loss associated with smaller lesions, unifocal, and presence of pseudodrusen. Systematic examination of structure and function may yield insights in selecting clinical trial endpoints to help demonstrate a functional benefit [15].

Intravitreal pegcetacoplan (Syfovre, Apellis Pharmaceuticals, Inc) is approved in the United States for the treatment of GA secondary to AMD. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency has recommended the refusal of the marketing authorisation of pegcetacoplan for GA, noting that while phase 3 trials showed that treatment slowed the growth of GA lesions, 'this did not lead to clinically meaningful benefits for patients'. Apellis Pharmaceuticals announced in response that it planned to seek a re-examination of the negative opinion, adding that it expects a final opinion in the fourth quarter of 2024.

Treatment with pegcetacoplan injection in patients with GA secondary to AMD demonstrated a visual function benefit in a prespecified microperimetry endpoint (OAKS study only), according to data from the GALE long-term extension study, presented at the Clinical Trials at the Summit meeting in June 2024 [16]. At 36 months, patients treated with both continuous monthly (p=0.0156) and every-other-month (p=0.1233) pegcetacoplan developed fewer new scotomatous points compared with patients from the sham crossover group (all p values nominal) (Figure 1).

Case selection and counselling are critical with current complement therapeutics approved for GA, noted Prof Chakravarthy.

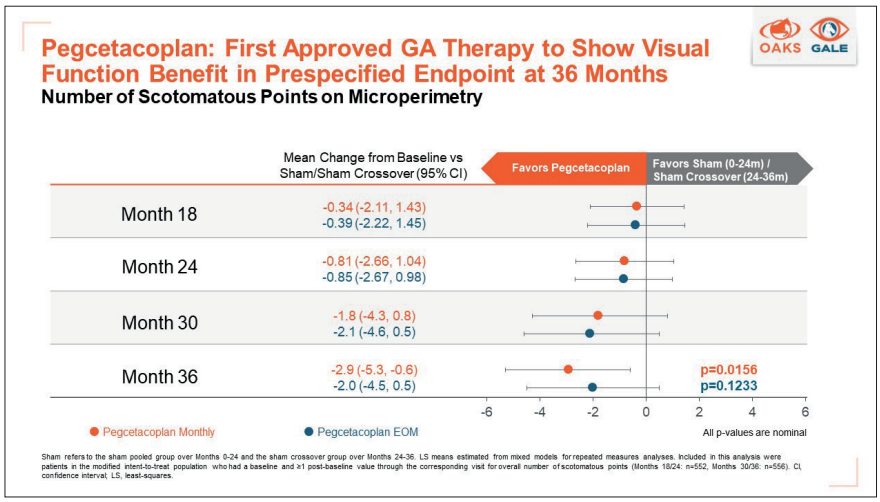

Figure 1: Thirty-six-month results from GALE phase 3 open-label extension study in geographic atrophy evaluating number of scotomatous points on microperimetry. Source: from Apellis Pharmaceuticals, Inc [16].

Clinicians should assess GA growth rate from past visits or by follow-up, consider patients with at least some useful central visual function (consider foveal occupancy of lesion), and juxta / extrafoveal GA with posterior margin close to the FAZ / foveal centre (and fellow eye with poor function due to GA).

Progress in Stargardt disease

Professor Andrew Lotery (University of Southampton) reviewed progress evaluating emerging therapies for Stargardt disease, a rare genetic eye disease usually caused by mutations in the ABCA4 gene. Lack of ABCA4 protein leads to accumulation of visual cycle byproducts (lipofuscin) and dysfunction of the RPE and subsequent photoreceptor degeneration [17]. Almost all patients with Stargardt disease become severely visually impaired or legally blind by the fourth to seventh decade of life.

Emerging therapies under investigation for Stargardt disease include gene therapy, pharmacologic therapies, and stem cell therapy, aimed at showing reduction of progression [18]. Intravitreal delivery of PEGylated ECO (a multifunctional pH-sensitive amphiphilic amino lipid) plasmid DNA (pGRK1-ABCA4-S/MAR) nanoparticles (PEG-ELNP) for gene therapy of Stargardt disease shows promise [19]. Topline results of the STARTT study showed oral remofuscin (Katairo GmbH) prevented retinal thinning in Stargardt disease patients, a protective effect that increased over time and was observed for both eyes [20]. Alkeus Pharmaceuticals announced positive interim results demonstrating no signs of disease progression in early-stage Stargardt disease patients treated with gildeuretinol acetate (ALK-001), a novel molecule created as a specialised form of deuterated vitamin A designed to reduce the dimerisation of vitamin A without disrupting vision.

Current management is focused on low visual aids and rehabilitation. Patients should be advised to avoid vitamin A or beta carotene supplements, avoid bright light, avoid hydroxychloroquine, consider Mediterranean diet and keep reasonably fit. Patients should be genotyped or referred for genotyping. Regular annual review with Heidelberg OCT and autofluorescence (± widefield) imaging is recommended.

Which anti-VEGF should I use?

The introduction of intravitreal anti-VEGF therapy for patients with neovascular AMD has allowed for improved prognosis and, in most patients, recovery and maintenance of visual function. There are now at least eight licensed intravitreal anti-VEGF drugs to choose from, including several ranibizumab biosimilars. Drug choice ideally should be based on securing maximal effectiveness with minimal intervention within an acceptable value and safety profile, balancing the interests of payers, providers and patients. Commissioning guidance from NHS England emphasises the need for reduction in unwarranted variation, maintenance of clinical choice, and making best use of NHS resources [21].

Professor Richard Gale (University of York and York and Scarborough Teaching Hospital NHS Foundation Trust) highlighted six key considerations in determining the 'best' option among currently available VEGF inhibitors for medical retinal conditions: shared decision-making; be aware of the safety profile; stick to the licensed posology; be aware of the pivotal clinical trial data; choice is disease specific; and discuss with patients and stakeholders expected injection frequency for initiation, likely injection frequency needed over two years, likely extension intervals, and safety profile (Table 2). New generation intravitreal therapies address clinicians' greatest need, namely that of meeting the capacity-demand gap challenge, argued Prof Gale. He added that definitions of active disease in clinical trial retreatment protocols impact reported durability outcomes. While all approved anti-VEGF agents are effective treatment options, he acknowledged the need for direct head-to-head studies to further clarify differences and similarities with respect to efficacy and durability.

Should we be planning to roll out Port Delivery System?

The Port Delivery System with ranibizumab (PDS) (Susvimo, Roche) is a refillable ocular implant for continuous delivery of a customised ranibizumab formulation into the vitreous, with in-clinic refill exchange once or twice a year. In the Archway phase 3 trial, PDS with ranibizumab refilled every 24 weeks was non-inferior to monthly ranibizumab injection in patients with neovascular AMD over nine months and two years [22]. Also, PDS represents the first continuous delivery treatment platform for DR / diabetic macula oedema (DMO) [23]. The Pagoda phase 3 trial in DMO met its primary endpoint, with PDS every 24 weeks (Q24W) shown to be non-inferior to monthly ranibizumab in best-corrected visual acuity (BCVA) change from baseline averaged over weeks 60 and 64. In the Pavilion phase 3 trial in DR without centre-involving DMO, PDS Q36W demonstrated superior efficacy compared with control, based on the proportion of patients achieving a ≥2-step improvement in ETDRS-Diabetic Retinopathy Severity Scale from baseline at week 52. Evaluations indicate that PDS is often preferred by patients over intravitreal injections.

Port Delivery System implantations have resumed in clinical trials globally, following redesign of the PDS implant and refill needle to optimise implant performance and mitigate the risk of septum dislodgement, and the overall safety profile is still evolving. Subject to future regulatory filings (EU, slated for ~2025/2026) and marketing authorisation(s), clinicians should be planning to roll out the PDS with ranibizumab for approved indications, but in a phased, controlled manner, with uptake likely driven by patient demand, commented Ian Pearce (St Paul's Eye Unit, Liverpool University Hospitals NHS Foundation Trust). The PDS device offers further potential as a platform for newer molecules specifically designed for continuous delivery.

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[All links last accessed June 2024]

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Declaration of competing interests: The author has provided consultancy services to Bayer AG, DORC International B.V., Johnson & Johnson Vision Care, Inc., Roche Products Ltd, and Thea Pharmaceuticals Ltd.