



The Yorkshire Retina Society supports clinical education, collaboration and excellence in relation to retinal disease. Membership of the Society comprises consultants with expertise in medical retina, trainee ophthalmologists and non-medical staff. As consultant members of the Society we welcomed the recent NICE guideline on Age-related macular degeneration, especially the clarity around the need to start treatment within 14 days and the extension of the visual acuity requirements to include eyes with visual acuity better than 6/12 or 6/96 or worse.<sup>1</sup> However, we are concerned with the statement that “no clinically significant differences in effectiveness and safety between the different anti-VEGF treatments have been seen in the trials considered by the guideline committee” and the implication that greater use could be made of the unlicensed medicine bevacizumab (Avastin) over the licensed preparations ranibizumab (Lucentis) and aflibercept (Eylea) as treatment option for neovascular age-related macular degeneration (nvAMD). The reasons for these concerns are listed below:

Clinical effectiveness and capacity: Both the CATT and IVAN studies found that bevacizumab was non-inferior to ranibizumab with regard to visual acuity outcomes when the treatment regimens were identical. However, monthly review/PRN treatment resulted in less gain in visual acuity than fixed, monthly injections, suggesting that, in the absence of other evidence, fixed, monthly injections would be the more appropriate course of action.<sup>2,3,4,5</sup> At the time that these studies were conceived, there was uncertainty about whether monthly review/PRN treatment would deliver the best visual acuity outcomes and the CATT and IVAN studies clearly identified that this was not the case, with this regimen proving inferior to monthly dosing.

Fortunately, more recent evidence has suggested that equivalent outcomes to fixed monthly treatment can be achieved with either fixed 2 monthly treatment with aflibercept or with a treat and extend regime, using either ranibizumab or aflibercept.<sup>6,7,8,9</sup> Guided by the available, high quality data, these treatment regimens are now current practice in our units and outcomes are audited annually. For bevacizumab, there is less evidence that a switch to either of these regimens will deliver similar outcomes. Both the LUCAS and GEFAL studies suggested that a greater number of bevacizumab injections, compared to ranibizumab, may be required to generate similar visual acuity gains.<sup>10,11</sup>

We do not feel that there is sufficient evidence to support the use of bevacizumab for nvAMD in a regime other than fixed, monthly injection when considering visual acuity outcomes. Switching to this regime is expected to double the number of injections required for nvAMD patients and requiring a major increase in capacity for re-consent, assessment and injection. The increase in medical and non-medical staffing to support this new regime will negate the potential cost savings from a switch to bevacizumab, assuming that the staff can be recruited in the required timescale.

Safety: Debate remains as to whether systemic side-effects of anti-VEGF therapy differ between bevacizumab, ranibizumab and aflibercept.<sup>13-17</sup> However, there is a



greater amount of published clinical trial data and confidence in the use of the licensed agents, ranibizumab and aflibercept. In terms of ocular adverse events, most of the risk is determined by the number of injections. A switch to a regime of either fixed monthly dosing or treat-and-extend with bevacizumab would increase the number of injections over the course of each year and add to the cumulative risk of ocular adverse events. In addition, there may be added risk of infectious endophthalmitis after bevacizumab injection, related to the need for compounding of the drug.<sup>17-18</sup>

Recent guidance from the Royal College of Ophthalmologists on the use of unlicensed medicines suggests that "...The prescriber may prescribe unlicensed medicines where, on the basis of an assessment of the individual patient, the consultant concludes, for medical reasons, that it is necessary to do so to meet the specific needs of the patient. When prescribing for this group of patients, the prescriber must exercise professional judgment that the patient must have an unlicensed medicinal product rather than a licensed product because the licensed product will not meet the clinical need of the patient."<sup>19</sup> In view of the likely need for additional injections of bevacizumab and the added risk associated with a greater number of injections, we cannot conclude that a switch to bevacizumab would meet the specific needs of patients with NvAMD.

Drug supply and compounding: At present, most NHS eye clinics obtain small amounts of bevacizumab for intra-vitreous injection from Liverpool and Broadgreen University Hospitals. Drug supply from the Moorfields Pharmaceuticals ended after concerns about an increase number of cases of endophthalmitis after intra-vitreous injection. Local NHS Trusts do not appear to have the resources or licenses to implement a new service and so there are concerns about the availability of bevacizumab for intra-vitreous injection from a reliable, NHS source. In addition the shelf-life of reconstituted bevacizumab is much less than for the other licensed products and so a robust supply chain is required.

The Consultant Ophthalmologists listed below in alphabetical order have endorsed this statement:

Seema Arora, Hull and East Yorkshire Hospitals NHS Trust  
Chris Brand, Sheffield Teaching Hospitals NHS Trust  
Helen Cook, Hull and East Yorkshire Hospitals NHS Trust  
Helen Devonport, Bradford Teaching Hospitals NHS Foundation Trust  
Narendra Dhingra, Mid-Yorkshire Hospitals NHS Trust  
Louise Downey, Hull and East Yorkshire Hospitals NHS Trust  
Richard Gale, York Teaching Hospital NHS Foundation Trust  
Faruque Ghanchi, Bradford Teaching Hospitals NHS Foundation Trust  
Rehna Khan, Calderdale and Huddersfield NHS Foundation Trust  
Nick Mawer, Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust  
Krishnappa Madhusudhana, Hull and East Yorkshire Hospitals NHS Trust  
Martin McKibbin, Leeds Teaching Hospitals NHS Trust  
Raj Mukherjee, Leeds Teaching Hospitals NHS Trust  
Roopa Setty, Bradford Teaching Hospitals NHS Foundation Trust  
Gavin Walters, Harrogate and District NHS Foundation Trust  
Naeem Zaman, Hull and East Yorkshire NHS Trust

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