Diabetic macular oedema: burden on an injection clinic and treatment-resistance to anti-vascular endothelial growth factor agents.

Muzammil A. Nahaboo Solim[1], Lyudmila Kishikova[1], Sreekumari Pushpoth[1]
1. Ophthalmology Department, The James Cook University Hospital, South Tees Hospitals, NHS Foundation Trust.
Corresponding author: m.nahaboosolim@nhs.net

BACKGROUND

- Diabetes retinopathy (DR) is a condition caused by chronic hyperglycaemia and is characterised by damage to the retinal microcirculation.
- With over 285 million individuals suffering from diabetes worldwide, DR is a leading cause of blindness[3]. According to a 2012 report, 93 million people suffer from DR and 21 million suffering from DMO globally[4].
- The threat to vision presents itself in two main ways. Firstly via the growth of new blood vessels, which can cause haemorrhage and subsequent retinal detachment as the blood vessels exert a tractional force on the retina. Secondly via a process termed diabetic macular oedema (DMO), which eventually leads to loss of central vision and blindness[1]. This is believed to be due to the breakdown of the blood-retinal barrier caused by the production inflammatory cytokines secondary to the chronic hyperglycaemia[2].
- Diabetic macular oedema (DMO) is a leading cause of blindness globally and many patients are resistant to intravitreal therapy.
- Our aims were to measure the DMO burden on an injection clinic and identify sub-responders and non-responders to anti-vascular endothelial growth factor (anti-VEGF) treatment in the real-world UK setting.

MATERIALS AND METHODS

- This was a retrospective observational study at a large tertiary hospital in the United Kingdom, over one month from June to July 2019 (n=55; 89 eyes)
- **Inclusion criteria**:
  - *diabetic patients – type 1 or 2*
  - *Receiving anti-VEGF injection*
  - *Age > 18 years*
- **Exclusion criteria**:
  - *Less than 12 months since first anti-VEGF injection*
  - *Co-existent chronic eye disease – e.g. inflammatory eye disease*
- The number of injections for DMO over one month was measured.
- Primary outcomes measures
- Central retinal thickness (CRT) using optical coherence tomography (OCT)
- Non-responders – CRT > 400µm
- Sub-responders - 250µm < CRT < 400µm
- Best-corrected visual acuity (BCVA) – Snellen chart observations converted to LogMAR

RESULTS

Table 1: Burden of DMO on an injection clinic over a 1-month compared with other main conditions requiring anti-VEGF injections

Anti-VEGF agents	Diabetic macular oedema N (%)	Age-related macular degeneration N (%)	Retinal vein occlusion N (%)	Others N (%)
Aflibercept	205 (15.5)	482 (36.3)	101 (7.6)	11 (0.8)
Ranibizumab	99 (7.5)	300 (22.6)	107 (8.1)	7 (0.5)
Bevacizumab	10 (0.8)	1 (0.1)	0	3 (0.2)
Total	314 (23.7)	783 (59.0)	208 (15.7)	21 (1.6)

Table 2: Baseline characteristics and clinical response to anti-VEGF treatment at 12 months

Characteristics	Values
Patients	55
Eyes	89
Age (years), mean (SD)	67.4 (13.0)
Males (%)	35 (65.5%)
Treatment duration, mean (SD)	38.9 (18.9)
Number of injections at 12 months, mean (SD)	7.7 (2.2)
>9 injections	33 (37.9)
7-8 injections	28 (32.2)
5-6 injections	18 (20.7)
<5 injections	8 (9.2)
Eyes with previous laser treatment (%)	25 (45.5%)
Anti-VEGF	
Aflibercept (Eylea®) (%)	46 (51.7%)
Ranibizumab (Lucentis®) (%)	42 (47.2%)
Bevacizumab (Avastin®) (%)	1 (1.1%)
Best-corrected visual acuity (ETDRS letters)	
At baseline, mean (SD)	68 (16)
At 12 months, mean (SD)	71 (14)
Central macular thickness (µm)	
At baseline, mean (SD)	405.9 (106.9)
At 12 months, mean (SD)	329.7 (83.6)
CRT < 250 µm at 12 months	13 (16.7%)
CRT 250-400 µm at 12 months	49 (62.8%)
CRT > 400 µm at 12 months	16 (20.5%)
Intra-ocular pressure (mmHg)	
At baseline, mean (SD)	16 (3)
At 12 months, mean (SD)	16 (4)

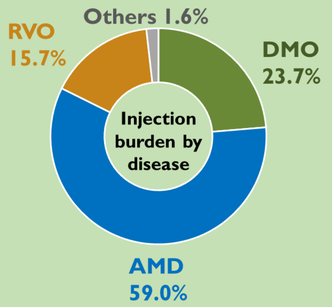


Figure 1: Proportions of injection by conditions for our ocular service

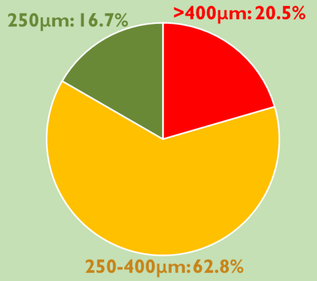


Figure 2: Central retinal thickness at 12 months after start of anti-VEGF therapy.

- Over one month, 314 out of 1326 (23.7%) injections were given for treatment of DMO.
- The mean treatment duration was 38.9 months.
- After looking at 60 patients (35 males, 94 eyes, mean age=67.4 years).
- At 12 months, there were 16 (20.5%) non-responders (CRT>400µm) and 49 (62.8%) sub-responders (CRT>400µm).
- At 12 months, the mean CRT reduction was 76.2µm. The mean increase in BCVA was 3 ETDRS letters.

KEY MESSAGES

- We highlight the 23.7% burden of DMO on our injection clinic, which will only worsen with the rising diabetes prevalence and which highlights the implications that DMO has in terms of cost and human resource requirement.
- The mean treatment duration of 38.9 months (range 12-99) further highlights the long-term impact that regular injections have on patients' lives and the ongoing service commitment required from the injection service provider.
- Despite receiving anti-VEGF therapy, we identified 62.8% sub-responder and 20.5% non-responder eyes.
- The mean CRT reduction (76.2µm) is about 35% of that achieved in major trials (250µm).
- Our findings raise the question of whether we need to begin anti-VEGF treatment when CRT is less than 400µm and consider agents such as intravitreal corticosteroids which are currently only recommended for phakic patients.

REFERENCES

1. Wang W, Lo ACY. Diabetic Retinopathy: Pathophysiology and Treatments. Int J Mol Sci. 2018;19(6):1816. doi:10.3390/ijms19061816
2. Bahrami B, Zhu M, Hong T, Chang A. Diabetic macular oedema: pathophysiology, management challenges and treatment resistance. Diabetologia. 2016;59(8):1594-1608. doi:10.1007/s00125-016-3974-8
3. Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. Eye Vis (London, England). 2015;2:17. doi:10.1186/s40662-015-0026-2
4. Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012;35(3):556-564. doi:10.2337/dc11-1909

Acknowledgements
I would like to express my gratitude to Ms S. Pushpoth and Dr L. Kishikova for their help and support for the data collection and this project.