Choice of anti-vascular endothelial growth factor therapy in the treatment of centre involving diabetic macular edema

Somdutt Prasad[1]

Treatment for diabetic macular oedema (DME) has been revolutionised over the last decade with the introduction of Anti-Vascular Endothelial Growth Factor (Anti-VEGF) agents into the retinal specialists armamentarium to treat this important cause of visual loss. Diabetic retinopathy (DR) remains the leading cause of visual loss in most parts of the world, with the sole exception of the United Kingdom where a systematic standardised national screening programme for diabetic retinopathy has succeeded in relegating it from first place as a cause for visual loss[1]. With a projected 642 million prevalence of diabetes by 2040[2], the management of diabetic retinopathy related visual loss will only increase both as a public health problem and a clinical workload issue.

In the pre-Anti VEGF era laser therapy remained the mainstay of treatment of DME, and whilst this was effective in reducing the amount of visual loss, very few patients actually gained vision on this treatment. The introduction of Anti-VEGF agents into treatment regimes for DME brought the realistic expectation of visual improvement to a over a third of the patients and the arrest of visual loss to the vast majority.

With a variety of therapeutic agents now available, choosing the right drug for the right patient is a dilemma every clinician has to face. This article aims to summarise the evidence available and make some recommendations to help clinical decision making.

Available agents for DME:

Two broad classes of agents are in current use for the treatment of DME. Anti-VEGF and Steroid agents (Ozurdex™, Illuvein™ and Retisert™). Generally Anti-VEGF agents are used as first line treatment, and intra-ocular steroids reserved for recalcitrant cases mainly due to concerns about cataract formation and raised intra-ocular pressure combined with the uncertainty about the number of years treatment will be required for. Anti-VEGF agents do not carry these risks and there is good evidence to show that by year 4 the need for anti VEGF agents has reduced to 0 or almost 0. Five Anti-VEGF drugs are currently available to treat DME; Ranibizumab, Bevacizumab, Aflibercept, the biosimilar Razumab and Ziv-Aflibercept. Ranibizumab and Aflibercept are licensed for intravitreal use for this indication and Bevacizumab, although off license, has the benefit of long term clinical experience and usage in randomised clinical trials (RCT) to support it's ongoing use. There is very limited experience with Razumab and no RCT evidence to support it's use in DME, and Ziv-Aflibercept has been used only is small case series with an unlicensed status. This article will therefore limit itself to discussing the three established agents, Ranibizumab, Bevacizumab and Aflibercept. Whilst there is a plethora of RCT evidence to support their use in DME, Protocol T of the DRCR.net compared these three drugs head to head in a large well designed RCT and is thus the most important evidence base upon which we can base our clinical decision making.

Results of Protocol T and learning points:

The 1-year study data, released in February 2015, showed that 2.0 mg afliber-cept (Eylea, Regeneron), 1.25 mg bevacizumab (Avastin, Genentech), and 0.3 mg ranibizumab (Lucentis, Genentech) provided impressive visual improvements for DME patients, and that, among patients with starting baseline visual acu-ity of 20/50 or worse as measured on an ETDRS chart, those treated with aflibercept showed significantly better visual acuity gains at 1 year compared with patients treated with bevacizumab or ranibizumab[3]. The two year data published in February 2016 showed that there was no difference

[1]Eye Department , AMRI Medical Centre, 97A, Southern Avenue, Kolkata, India.
Corresponding Author : Dr. Somdutt Prasad, E-mail: somprasad@gmail.com
Received on : 01/12/2016, Revision accepted on : 10/12/2016
Conflict of Interest : None, Financial Disclosure : None

between Ranibizumab and Aflibercept in terms of visual outcomes overall, or in the better seeing or poorer seeing subgroups of eyes at entry[4].

Before we get to looking at the visual outcomes, it is relevant to look at the overall treatment burden. The promise of Aflibercept was that it would reduce the number of injections required, but this was not borne out in Protocol T. The median number of injections was not significantly different among the treatment arms or in other words the burden of treatment isn't less with one agent versus another. So treatment burden is not a factor to help the choice of agent. Again, before extrapolating the Protocol T results to general clinical practice, we need to keep in mind that the 0.3 mg of Ranibizumab (The FDA licensed dose for DME in the USA) was used in the study, whereas 0.5mg is the dose used across the rest of the world. Also the Bevacizumab used was compounded under strict quality controlled conditions, in single use glass vials, a preparation which may not be available to many practitioners in many parts of the world or indeed to almost all practitioners across the world in a non-clinical trail setting.

At year 1, the mean change in visual acuity in the overall population was comparable between the three drugs—about 13 letters for aflibercept, almost 10 let-ters for bevacizumab, and about 11 letters for ranibizumab—and deemed not to be clinically meaningfully different.However, in the subgroup with a visual acuity less than 69 let-ters (about 20/50 or worse), a statistical difference was seen: there was an almost 19-letter gain for aflibercept, about 12 letters for bevacizumab, and just over 14 letters for ranibizumab.And the mean change in central subfield thickness, for the over-all population, was about 170 ìm for aflibercept, compared to 100 ìm with bevacizumab and 150 ìm with ranibizumab.The rates of most ocular and systemic adverse events were similar across the three groups. The conclusion at year 1 was that Aflibercept provided quicker and better visual outcomes in eyes with poorer vision at entry.

When the 2 year results were published, there was no clinically important difference in the visual outcome among the three different drugs and approximately 80% of the patients in each cohort continued to require some injections in year 2.The results from Protocol T at 2 years were very interesting, because whatever differences were picked up in the first year of the trial completely disappeared by the second year. In the overall group of patients, there is no statistically sig-nificant difference between aflibercept and ranibizumab 0.3 mg in terms of visual gains.In year 2, vision gains were 12.8 letters for aflibercept, and 12.3 letters for ranibizumab; bevacizumab remained at 10 letters. Looking at the proportion of patients who gained or lost 10 or 15 letters, the year 2 differences among the three drugs were not statistically significant.Evaluating the data by subgroup analysis, for those with baseline visual acuity of 20/50 or worse (letter score <69), 76% of those in the aflibercept group and 71% of those in the ranibi-zumab group gained 10 letters, with 58% in the aflibercept group and 55% in the ranibizumab group gaining 15 letters, respectively. It may be of interest that 5% of the aflibercept group but only 2% of the ranibi-zumab group lost more than 10 letters at year 2. For those patients who had good baseline vision (20/32 to 20/40 or a letter score between 78 and 69), in the first year there were no differences among the groups in visual gains. At the end of year 2 the mean improvement showed ranibi-zumab to be approximately a letter better than aflibercept: the mean improvement was 7.8 letters for aflibercept, 6.8 letters for beva-cizumab, and 8.6 letters for ranibizumab, bot a statistically significant difference.

Discussion:

It is interesting to speculate why the results of year 1 were so different from that of year 2. Diabetes is a chronic disease and it is important to look at long term results rather than month by month or year by year results. If we look at the year one results the differences shown between Aflibercept and Ranibizumab had very large confidence intervals, so may not have reflected a true difference, on the other hand ranibizumab rally at year 2 maybe a result of a return to the mean. Generally if you wait long enough you see a return to the mean. The issue of 0.3mg Ranibizumab vs 0.5 mg Ranibizumab may also have had an impact on the results. Signals within the RISE and RIDE trials point out the possibility that a 0.5-mg dose is more powerful than a 0.3-mg dose[5], including data that show that patients in the 0.5-mg ranibizumab arm received less rescue laser during the RISE and RIDE studies than those in the 0.3-mg arm. The year 2 results make sense in the context of compa-rable trials like VIVID and VISTA[6], RIDE and RISE, RESTORE[7], and Protocol I[8] from which we expected that ranibizumab and aflibercept should behave in a very similar way, but that wasn't the case with the year 1 results, which suggests that he year 1 results were an outlier and the year 2 results, being more consistent with other RCTs is more likely to reflect the clinical reality.

Conclusion:

Protocol T delivered good news for patients and doctors: it showed that all three anti-VEGF agents used to treat DME are effective, meaning that retinal specialists will continue to have a menu of options when initiating DME treatment. Local availability and economic considerations will no doubt guide treatment decisions in different healthcare settings, but overall our patients will benefit equally, whether we choose Ranibizumab or Aflibercept as our first line of treatment and perhaps a little less in terms of visual outcome with Bevacizumab.

Reference:

1. Quartilho A, Simkiss P, Zekite A, Xing W, Wormald R, Bunce C. Leading causes of certifiable visual loss in England and Wales during the year ending 31 March 2013.Eye (Lond) 2016;30:602-7.
2. IDF diabetes atlas - 7th edition. http://www.diabetesatlas.org/. Accessed 15 November 2016.
3. Wells JA, Glassman AR, Ayala A, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med 2015; 372: 1193-1203.
4. Wells JA, Glassman AR, Ayala A, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from the comparative effectiveness randomized clinical trial [published online ahead of print February 27, 2016]; Ophthalmology.
5. Bressler NM, Varma R, Suñer IJ, Dolan CM, Ward J, Ehrlich JS, Colman S, Turpcu A; RIDE and RISE Research Groups.Vision-related function after ranibizumab treatment for diabetic macular edema: results from RIDE and RISE. Ophthalmology 2014; 121:2461-72.
6. Heier JS, Korobelnik JF, Brown DM, et al. Intravitreal Aflibercept for Diabetic Macular Edema: 148-Week Results from the VISTA and VIVID Studies. Ophthalmology2016; 123: 2376-85.
7. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 2011; 118: 615-25.
8. Diabetic Retinopathy Clinical Research Network1; Writing Committee, Aiello LP, Beck RW, Bressler NM, Browning DJ, et al.
9. Rationale for the diabetic retinopathy clinical research network treatment protocol for center-involved diabetic macular edema. Ophthalmology2011;118:e5-14.

Cite this article as:
Prasad S. Choice of anti-vascular endothelial growth factor therapy in the treatment of centre involving diabetic macular oedema. Current Indian Eye Research 2016; 3:93-5.