Editorial

What is the best anti-vascular endothelial growth factor agent for the treatment of diabetic macular edema? Review of the 2-year results of Diabetic Retinopathy Clinical Research Network Protocol T

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Diabetic macular edema (DME) remains a main concern in diabetic patients, due to potential visual impairment with any level of diabetic retinopathy. The first study to provide a treatment option for these patients was The Early Treatment Diabetic Retinopathy Study (ETDRS), using laser therapy to reduce moderate vision loss by approximately 50% in patients defined as having clinically significant macular edema (1). Despite the fact that prevention of visual loss is crucial, visual improvement is another important goal. Therefore, the focus of research in the past years has been shifted to the use of anti-vascular endothelial growth factor (VEGF) therapy to treat DME, with focal laser no longer considered as first line therapy. With excellent results reported in previous studies, and only rare adverse events, it is becoming clearer that anti-VEGF therapy will play an increasing role in DME treatment.

A variety of intravitreal anti-VEGF agents are currently available, with others under study. Randomized studies comparing between those medications were previously published in patients with exudative age-related macular degeneration (AMD) (2). In July 2016, the Diabetic Retinopathy Clinical Research Network (DRCR.net) published their two years results for the comparative effectiveness of aflibercept, bevacizumab and ranibizumab for center-involved DME (3).

One year results from that study demonstrated that despite the fact that all agents, on average, improved visual acuity (VA), differences in their relative effectiveness were observed when patients were stratified dependent on their initial VA (4). When baseline VA impairment was mild (20/40 vision or better), no differences on average were identified. However, at worse levels of baseline VA impairment, aflibercept was found to be more effective. Additionally, the worse the initial VA, the greater the relative advantage of aflibercept over the other two agents. Therefore, two years results were impatiently anticipated, by care givers and diabetic patients, as well as by the pharmaceutical industry, in order to discover if those differences were maintained.

The study was conducted as a randomized multi-center clinical trial, in 89 sites. Patients were only included if they were at least 18 years old, with type 1 or type 2 diabetes. Other inclusion criteria for the study eye included VA in the range of 20/32 to 20/320, central-involved DME on clinical exam, central subfield (CSF) thickness ≥412, as measured with stratus optical coherence tomography (OCT), and no history of an anti-VEGF treatment for DME in the past 12 months or any other DME treatment in the past 4 months. Overall, 660 participants, 53% men, were included in the study, with mean age of 61±10 years.

Therefore, conclusions from this study cannot actually be applied for patients with worse or better VA and for patients already treated with anti-VEGF during the last year.

Main outcome was defined as the change in VA with either aflibercept 2.0 mg, bevacizumab 1.25 mg, or ranibizumab 0.3 mg. Other measured outcomes included adverse events, retreatment frequency and need for laser treatment. Study design dictated visits every 4 weeks during the first year and every 4 to 16 weeks during the second year, depending on treatment course. However, retreatment was based on VA and OCT criteria, and not monthly as still customized in many centres for the first injections. Focal/grid laser treatment were optional if DME persisted and was not improving, starting at 6 months.

Of special notice is the fact that participants were informed of the primary results and their group assignment following the publication of the first year results in February 2015. At that point decision could be made to switch to a non-study anti-VEGF agent, although discouraged.

The rate of patients completing 2 years in the study was high, with almost 90% in study groups. No differences were observed in the mean number of visits in the second year (9.4, 9.3, 9.3), the median number of injections in the second year [5, 6, 6] or overall number of injections [15, 16, 15] between aflibercept, bevacizumab or ranibizumab respectively.

Laser treatment was performed less frequently in the aflibercept treated eyes in year 2, similar to 1 year results. Over the two years, only 41% of patient treated with aflibercept required protocol indicated laser compared to 64% in bevacizumab group (P<0.001) or 52% in ranibizumab group (P=0.04). The differences between the latter two agents were statistically significant as well, with P=0.01.

Those impressive differences in the need for laser between the groups were probably related to the differences in the improvement of CSF, as will be shown below. It is therefore reasonable to assume that investigators followed their study instructions for laser treatment indications. However, laser may introduce a bias if it reduces VA, as it was performed much more frequently in the bevacizumab group.

VA improvement at 2 years was seen with all three agents. During the second year of the study, the number of injections decreased by approximately 50% as well as the amount of laser performed in all study groups. Among eyes with better baseline VA (20/40 or better) no differences in regards to vision outcomes were observed between the three agents.

For the overall group, mean change in VA was only significantly better for patients treated with aflibercept (+12.8 letters) compared to bevacizumab (+10 letters), P=0.02. Change of +12.3 letters after two years of treatment with ranibizumab was not statistically different from aflibercept (P=0.47) or bevacizumab (P=0.11).

Among eyes with worse baseline VA (20/50 or worse) a superior outcome was identified for aflibercept, on average, compared with bevacizumab, although the difference was milder than that seen after 1 year.

The difference in VA gain between aflibercept and ranibizumab noted at 1 year results, not only decreased, but was also no longer statistically significant. Therefore, based on this current study, it is possible to conclude patients with DME will achieve the same VA gain with either aflibercept or ranibizumab after 2 years of treatment, with any level of baseline VA. However, patients with worse baseline VA, will have the advantage of better 1 year results if treated with aflibercept rather than with ranibizumab.

Further statistical analysis was performed for the 2-year results to compare between treatment groups in regards to visual gain or loss of 10 or 15 letters. No significance was observed for either treatment for either measure. Of special notice is the fact that this analysis was a major issue with 1 year results, as patients treated with aflibercept were much more likely to gain 15 letters. Assuming gain of vision is of paramount importance, as this is how patients perceive improvement in their visual function, we can argue that disappearance of that advantage makes aflibercept equal to the other two agents.

When measuring the mean change in CSF from baseline with OCT, an advantage for either aflibercept (–171 μ) or ranibizumab (–149 μ) over bevacizumab (–126 μ) was observed (P<0.001 and P=0.001 respectively), with no differences between the first two agents (P=0.08). Those statistically significant differences findings are maintained in the better baseline VA subgroup, but not the worse VA group.

In the subgroup of patients with baseline VA of 20/50 or worse, statistical significance differences were observed only between the two groups treated with aflibercept or bevacizumab, with a mean decrease of 211 letters compared to 174 respectively (P=0.01).

Therefore, in the overall group and the better VA group, one can conclude that if you are looking to have less fluid in OCT, probably translated to lesser need for laser, one might choose either aflibercept or ranibizumab.

A major issue that rises from the differences between

1 year and 2 years results is the relevance of short term results for patients with a chronic and long lasting disease. An argument can be made that when treating patients with DME, the long-term effects of the treatment are the most important results. First year results have only little influence on the patient fighting diabetic retinopathy through his lifespan. However, a counter argument is that if you can give your patients faster results, why offer anything else?

Another important dispute, raised frequently by the study critics, is the dosage used for ranibizumab in this study. The dose given was the lower dose of 0.3 mg, as approved for use in the United States. However, worldwide the FDA-approved version of 0.5 mg ranibizumab is far more common. The question is whether it is possible that under-dosing influenced the results, as there had never been a prior study that investigated the use of 0.3 mg ranibizumab for as-needed (PRN) treatment schedule and not monthly. Furthermore, previous data from RIDE and RISE studies show there were approximately one-third more patients in the group treated with 0.3 mg dose who needed focal laser rescue treatment at 24 months compared with the 0.5 mg dose of ranibizumab (5,6). An opposing argument is that RIDE and RISE studies have proven that patients treated with either ranibizumab 0.3 mg or ranibizumab 0.5 mg had the same VA gain results. Yet we need to remember that the above studies were actually not powered to answer questions about the differences in dosing, only designed to answer the question whether treatment was better than no treatment at all.

The large differences in costs for the three agents are of important matter. As aflibercept and ranibizumab are 20 to 30 times more expensive than bevacizumab, its superiority should be highly justified by data. Given the fact that the use of all three agents resulted in improvement in VA, the question is of high relevance. In fact, the data suggests that we can use bevacizumab as first line therapy in patients with good baseline VA (20/40 or better), as visual gain was recorded the same for other agents, with only OCT results inferior for that drug. For all other patients, perhaps constituting the larger portion of patients seen at outpatient clinics, the question remains. It is our opinion that each DME patient should be aware of the possible efficacy differences between those agents, while deciding whether they are substantial enough for him to consider the high costs. However, in a system where the ophthalmologist or the health insurance system have to decide which agent to choose, one can rest assure treating all his DME patients with bevacizumab will benefit them greatly, while saving money for other indications in the health system.

Regarding safety, ocular adverse events were similar in all three agents, with elevated intra-ocular pressure being the leading event, and only one injection related infectious endophthalmitis in each group.

The most unpredictable findings, not demonstrated consistently in previously reported clinical trials, were found in this study in regards to systemic safety of ranibizumab. Systemic rates of anti-platelet trialists collaboration (APTC) events, as defined by the study protocol, were higher in that group of patients, with 12% of patients experiencing any APTC event compared to 5% or 8% in the aflibercept (P=0.047) and bevacizumab (P=0.2) groups respectively. Those higher rates consisted of more non-fatal strokes and vascular deaths in the ranibizumab group. With further analysis, including adjustment for a history of prior stroke or myocardial infarction (MI) and other potential confounders, P values increased slightly, with no substantial change in the results.

One explanation for that is that although this was a randomized study, the cohorts were not completely balanced. A higher incidence of patients with prior coronary artery disease can be seen in the ranibizumab group. When adjusting for that imbalance, there is no longer any significant increase in the risk of APTC events for ranibizumab. Therefore, the 12% rate of APTC events in ranibizumab participants in the current study is questionable. It is important to mention that the inconsistency with prior studies, including DRCR.net Protocol I (7% event rate) and a recent meta-analysis that did not identify an increased risk of major cardiovascular or hemorrhagic events with ranibizumab compared with control, is remarkable (7,8). Therefore, the implications of that finding are not clear, warranting continued evaluation. Our personal opinion is that the inconsistency is too remarkable to conclude ranibizumab possess a true considerable elevated risk for cardiovascular events. It is most probable that present study was underpowered to give an accurate assessment of the risk of APTC events or other systemic risks.

In summary, treatment with all three agents studied in this present study showed improvement in vision and macular thickness in patients with DME. The 2 years' results demonstrate that with these long standing chronic diseases, we need to study the long term follow up results with our treatments, in order to learn patient's outcome over time rather than rely only on short term outcomes. In a cost effectiveness study performed by the DRCR net

on this study, aflibercept and ranibizumab were not cost-effective relative to bevacizumab for treatment of DME, unless their prices decrease substantially (9).

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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