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Improvement or Worsening in Diabetic Retinopathy Through 2 Years in a Randomized Clinical Trial Comparing Aflibercept, Bevacizumab, and Ranibizumab

- Susan B. Bressler, MD

OBJECTIVE To compare changes in diabetic retinopathy severity improvement and worsening through 2 years, while receiving repeated intravitreous injections of aflibercept, bevacizumab or ranibizumab for DME.

PURPOSE Anti-vascular endothelial growth factor (anti-VEGF) therapy for diabetic macular edema (DME) increases rates of diabetic retinopathy (DR) improvement and reduces rates of DR worsening in randomized clinical trials when compared with treatments that do not include anti-VEGF therapy. A pre-planned secondary analysis of Protocol T (DRCR.net) explores if these effects differ across anti-VEGF agents.

METHODS 650 eyes with center-involved DME and vision impairment (Snellen equivalent 20/32-20/320) were randomized to 2-mg aflibercept (A), 1.25-mg bevacizumab (B), or 0.3-mg ranibizumab (R) up to every 4 weeks through 2 years following a structured re-treatment protocol(Protocol T). Percentages with retinopathy improvement at 1 and 2 years and cumulative probabilities for retinopathy worsening through 2 years were compared between treatment groups without adjustment for multiple outcomes. Outcomes were assessed separately for eyes with non-proliferative DR vs. proliferative DR at study entry. A post hoc analysis explores sustained DR improvement at 2 years among those that had improvement at year 1.

RESULTS 495 eyes enrolled with non-proliferative DR (NPDR) and 155 eyes with PDR. At 1 year, among 423 evaluable NPDR eyes, 31%, 22%, and 38% treated with aflibercept, bevacizumab, and ranibizumab had improvement of DR severity (P=0.004 for A-B, P=0.012 R-B, P=0.51 A-R). At 2 years, there were no apparent treatment differences. For evaluable eyes with PDR at baseline (N=93), 1-year improvement rates were 76%, 31% and 55% for aflibercept, bevacizumab, and ranibizumab, respectively (P<0.001 for A-B, P=0.089 for R-B, P=0.017 for A-R). These rates and treatment group differences appeared maintained at 2 years. Despite an average reduction in injections in year 2, 59% of NPDR and 70% of PDR eyes that manifested improvement at 1 year, maintained improvement at 2 years. Two-year cumulative rates for retinopathy worsening ranged from 7%-10% and 17%-26% among the anti-VEGF groups for NPDR and PDR eyes, respectively. No definitive differences were noted for DR worsening.

CONCLUSION Within 2 years, NPDR eyes receiving anti-VEGF for DME may have DR improvement. Bevacizumab had the lowest improvement rate at 1 year. In the smaller PDR subgroup, aflibercept had the highest improvement rate at 1 and 2 years. All 3 anti-VEGF agents were associated with low rates of DR worsening. These additional outcomes might be considered when choosing an anti-VEGF agent to treat DME.

TAKE HOME MESSAGE Within two years, eyes receiving anti-VEGF for DME may experience improvement in diabetic retinopathy. All three agents were associated with low rates of DR worsening without treatment differences.

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

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Inhibition of Diabetic Retinopathy Progression by 0.2 ug/day Fluocinolone Acetonide Implants: A Fellow-Eye Controlled Analysis

- Raymond Iezzi, MD, MS
- Ken Green
- barry kapik, MS

OBJECTIVE To measure the efficacy of fluocinolone acetonide (FAc) 0.2 µg/day intravitreal implants in slowing the progression of diabetic retinopathy (DR).

PURPOSE Inter-subject treatment comparisons for DR can be confounded by systemic factors influencing DR severity such as acute and chronic control of serum glucose and systemic blood pressure. To determine if 0.2 µg/day FAc implants slow diabetic retinopathy (DR) progression, we conducted a fellow eye controlled analysis of the FAME datasets to control for systemic risk factors associated DR progression.

METHODS FAc treated patients in the prospective FAME trials with matching bilateral baseline ETDRS multi-step DR severity scores (DRSS) were included in this 36-month analysis. Fellow-eye comparison of ≥2 step and ≥3 step worsening in DRSS and progression to proliferative DR (PDR) was performed using a McNemar's test that accounted for the correlation between the two eyes within each patient. Progression was classified as follows: both eyes progressed, only the FAc treated eye progressed, only the

fellow eye progressed, or neither eye progressed. The McNemar's test was performed on these groups at a 0.050 level of significance to determine if the FAc treated and fellow eye frequencies were equal.

RESULTS For the overall population (n=184) 36-month, progression to PDR in the FAc treated eyes had an incidence of 12.5% versus 22.3% in the fellow eye (p = 0.0027). In patients with moderately severe to severe NPDR (n=83), progression in the FAc treated eyes had an incidence of 15.6% versus 30.1% in the fellow eye at 36-months (p=0.0105). The incidence of DR worsening based on a ≥3 step change was 0.5% versus 3.8% for FAc treated eyes and fellow eyes, respectively, (p=0.0143, n=184) and 5.5% versus 10.4% (p=0.0290, n=184), respectively, based on a ≥2 step change at 36-months.

CONCLUSION The FAME trials allowed for a fellow eye controlled analysis of the effects of FAc implants on DR progression. Pharmacodynamic effects were observed within treated eyes, without measurable systemic corticosteroid levels and without fellow-eye crossover effects. Continuous delivery of submicrogram FAc doses slowed the progression of PDR and NPDR in patients with matched baseline DRSS.

TAKE HOME MESSAGE Submicrogram daily doses of sustained-release Fluocinolone Acetonide inhibit the progression of diabetic retinopathy.

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

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Long-Term Visual Acuity Response in Early Nonresponders Treated With 0.2µg/day Fluocinolone Acetonide Implants in FAME Study

- Daniel B. Roth, MD
- Ken Green

OBJECTIVE To analyze the month 36 visual acuity outcomes of patients treated with 0.2µg/day fluocinolone acetonide (FAc) in FAME study in early non-responders at week 6, using anatomical or visual criteria.

PURPOSE The 0.2 ug/day FAc implant is the only approved therapy for DME that continuously delivers therapy for 36 months. Although some eyes do not show an early anatomic or visual response, it is feasible that some of these patients may convert to responders over time. This could provide important clinical insight related to the treatment of DME with 0.2 ug/day FAc.

METHODS Patients treated with 0.2 ug/day FAc implants were analyzed using change in BCVA (best-corrected visual acuity) and CST (central subfield thickness). Criteria for defining response at week 6 was: at least a 5 letter improvement in BCVA or at least a 50 micron reduction in CST. Change in BCVA at month 36 was evaluated for those patients deemed non-responders at week 6, using either BCVA or CST independently. Use of

additional laser or alternative therapies was evaluated to assess their contribution to conversion from early nonresponse to long-term response.

RESULTS Using change in either CST or BCVA at week 6, patients separated into two clearly defined categories of responders vs. non-responders, which were maintained through 36 months. At month 36, when the non-responder population was assessed for improvement in BCVA (increase of 5 letters or more), stability of BCVA over 36 months (change of BCVA between +4 to -4 letters) or loss of BCVA (decrease of 5 letters or more), 50% of patients were responders by month 36 and 25% had stable vision. This was evident whether non-response was defined based upon anatomic or visual criteria. When addition of laser or alternative therapies were considered, these could not account for the conversion from early non-response to becoming long-term responders.

CONCLUSION In FAME, most patients who are classified as early non-responders at week 6 achieve stable or improved BCVA by month 36, with quarterly visits and a mean of 1.3 injections. Recent analyses on anti-VEGF therapy from Protocol I have shown that some patients convert from being non-responders to responders after 3 years, however, this is achieved with intensive visits and multiple injections.

TAKE HOME MESSAGE The 0.2µg/day fluocinolone acetonide implant continuously delivers therapy for 36 months, and even though some eyes do not respind initially at the 6 week follow-up, 75% of eyes will have stable or improved visual acuity at 36 months.

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

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Baseline Macular Perfusion Impact on Visual and Anatomic Outcomes During DME Management: Analysis of the VISTA Phase 3 Study

- Charles C. Wykoff, MD, PhD

OBJECTIVE To explore the effect of baseline macular perfusion status on visual and anatomic outcomes in patients with DME treated with intravitreal aflibercept injection or laser.

PURPOSE To evaluate the influence of baseline macular perfusion status on best-corrected visual acuity (BCVA) and central retinal thickness (CRT) treatment outcomes in patients with DME.

METHODS VISTA randomized 466 DME patients to intravitreal aflibercept injection (IAI) 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks following 5 monthly doses (2q8), or laser. Retinal perfusion was evaluated by posterior pole fluorescein angiography based on the binary presence or absence of retinal non-perfusion (RNP) in quadrants intersecting at the optic nerve head by an independent masked reading center. Three groups were identified: 1) RNP in the quadrant representing the macula (Q4); 2) RNP absent in Q4 but present elsewhere; 3) RNP absent all quadrants. Mean change in BCVA

and CRT for the three subgroups are reported. Patients who received rescue treatment were censored at time of rescue.

RESULTS At baseline, Group 1 included 75.7%, 66.2%, and 73.7% of laser (n=136), 2q4 (n=133), and 2q8 (n=138) patients, respectively. The corresponding proportions in Groups 2 and 3 were 7.0%, 4.6%, 3.2% (n=129,130,126); and 17.8%, 29.2%, 25.4% (n=129,130,126), respectively. Baseline BCVA in Group 1 were 58.6, 57.4, and 57.9 letters in the laser, 2q4 and 2q8 patients. The corresponding BCVA in Groups 2 and 3 were 63.3, 60.3, 64.8 letters and 61.7, 62.7. 61.5 letters, respectively. Baseline CRT in Group 1 were 513.3, 493.4, and 494.3 μm in the laser, 2q4 and 2q8 patients. The corresponding CRT in Groups 2 and 3 were 366.2, 390.2, 393.5 μm and 445.4, 469.6, 466.9 μm, respectively. Mean changes in BCVA and CRT at weeks 52 and 100 for the corresponding groups are shown in Table 1.

CONCLUSION The majority of the DME patients in the VISTA study presented with RNP in the macula. On average, these patients had lower baseline BCVA and thicker CRT than those without RNP in the macula. Irrespective of baseline perfusion status, improvement in BCVA and CRT were observed in all subgroups through week 100 with IAI treatment.

TAKE HOME MESSAGE In VISTA, improvement in BCVA and CRT were observed in all subgroups through week 100 with treatment with IAI for DME, regardless of baseline macular perfusion status

Table 1. Mean Changes in BCVA and CRT at Weeks 52 and 100 in Groups 1, 2, and 3.

Baseline Macular Perfusion Status	Mean Change BCVA (letters, LOCF)					
	Laser		2q4		2q8	
	52	100	52	100	52	100
Group 1	-9.2 (n=103)	0.1	12.3 (n=98)	12.4	11.1 (n=98)	11.7
Group 2	6.6 (n=9)	7.6	14.5 (n=6)	15.2	16.5 (n=4)	16.5
Group 3	-0.4 (n=23)	1.0	12.7 (n=38)	9.9	8.7 (n=32)	9.3
	Mean Change CRT (microns, LOCF)					
	Laser		2q4		2q8	
	52	100	52	100	52	100
Group 1	-90.2	-101.2	-203.1	-205.3	-201.4	-207.3
Group 2	-39.1	-46.6	-90.2	-98.8	-79.3	-86.3
Group 3	-27.9	-31.6	-157.9	-175.8	-160.7	-177.2

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

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Slurry Kenalog®: A Lower Cost, Quick and Easy Alternative for Long-Term Intraocular Steroid Delivery

- Susan M. Malinowski, MD
- Ramsudha Narala

OBJECTIVE Slurry Kenalog® (centrifuge concentrated triamcinolone acetonide 40mg/0.1ml) is an easily reproducible, safe and cost effective alternative to long term intraocular steroid delivery.

PURPOSE To demonstrate the safety, efficacy and viability of intravitreal Slurry Kenalog® (triamcinolone acetonide) to treat macular edema at low cost and with reduced treatment burden.

METHODS *Slurry Kenalog*® was prepared by centrifuging 1.0 cc of Kenalog® (40mg/ml) into a 0.1 cc pellet. Retrospective review of all consecutive patients who received Slurry Kenalog® 0.1 cc (effectively 40mg/0.1ml) intravitreally for cystoid macular edema (CME), with a minimum follow up of 9 mos from the last injection. Indications for treatment included CME due to diabetes (62%), CRVO (16%), uveitis (11%), radiation retinopathy (5%), infectious endophthalmitis (3%), and BRVO (2%). Sixty-three eyes of 52 patients received 257 injections between June, 2009 and December, 2016, (average follow up 3.25 years/eye). Duration of effect was based upon recurrence of edema by OCT from the last injection.

RESULTS Slurry Kenalog® lasted an average of 8.4 months from a single intravitreal injection (range 2-24 months), as measured by recurrence of macular edema on OCT. In eyes with prior vitrectomy, the duration was 5.4 months, and without prior vitrectomy 9.1 months. Eight of 11 phakic eyes (73%) underwent cataract extraction. Thirteen eyes (21%) developed a steroid response (defined as a change of 10 mm Hg

from baseline). Ten (16%) were controlled on 2 or fewer drops, 2 (3%) were monitored, and one eye (1.6%) required a trabeculectomy. There were no cases of infectious endophthalmitis and just one case of nonsterile inflammation, which resolved without sequelae.

CONCLUSION Slurry Kenalog® has a long, average duration of effect of 8.4 months. There were no serious adverse events. The typical steroid associated side effects were average or lower than comparative, long term, implantable steroid preparations. Assuming an average of 2.9 injections over 2 years, the medication cost would be $29, with reduced treatment burden for both the physician and the patient.

TAKE HOME MESSAGE Slurry Kenalog® has a long average duration of effect of 8.4. The typical steroid associated side effects were average or lower than comparative, long term, implantable steroid preparations. There were no serious adverse events.

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board