Ranibizumab in Diabetic Macular Edema; Level 1 and Level 2 Studies Findings

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ABSTRACT

INTRODUCTION. Ranibizumab is an anti-VEGF antibody widely used in DME treatment.
MATERIALS AND METHODS. We conducted a literature search using the keywords "diabetes", "diabetic retinopathy", "diabetic macular edema", "pathophysiology", "VEGF", "treatment", "anti-VEGF", "ranibizumab", "lucentis" with limitation of English language. The articles published between 2006–2016 years and we reviewed level I and level II studies.
RESULTS. Review from several level I and level II intravitreal ranibizumab injection studies suggests that ranibizumab is an anti-VEGF that effectively used in DME treatment. Comparison with other anti-VEGF also suggest that ranibizumab is effective for DME patients for over 2 years treatment.
CONCLUSIONS. Ranibizumab monotherapy and/or combination with laser is safe and effective for DME patients for over 2 years treatment.

KEY WORDS: diabetic macular edema, anti VEGF, ranibizumab

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INTRODUCTION

Diabetes is considered as chronic disease and diagnosed by observing the increase of blood glucose level.1 High blood glucose can lead to different organ damage including the eyes.[1, 2]

Many aged 20–74 years diabetes develop some form of eye disease (Diabetic Retinopathy), with potential loss of vision [1–4].

Based on 2012 study, 35% people with diabetes had some form of Diabetic Retinopathy and 7% had Proliferative Diabetic Retinopathy, 7% had Diabetic Macular Edema, and 10% were affected by vision-threatening stages [5].

Diabetic Macular Edema (DME) is a common complication of diabetic retinopathy which is characterized by a swelling of the macular area due to leakage of proteins through vascular walls following the development of intracellular as well as extra-cellular hypertonic environments after an ischemic event [6, 7].

Vascular Endothelial Growth Factor (VEGF) is a major mediator of blood retinal barrier (BRB) breakdown and the development of macular edema.6 VEGF is a disulfide-bound homodimer glycoprotein. It is one of the most important regulators of vasculogenesis and angiogenesis. An inflammation-induced breakdown of the BRB is mediated by VEGF via binding to leukocytes and inducing their recruitment to the site of the inflammation. There are 5 types of VEGF which are VEGF-A, VEGF-B, VEGF-C, VEGF-D and VEGF-E. The VEGF that is involved in the development of macular edema in the eyes is mainly VEGF-A [7].

Therefore, currently, anti-VEGF treatment is one of the promising treatment of visual loss in DME patients [6, 8].

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MATERIALS AND METHODS

We conducted a literature search on PubMed®, Google Scholar™, and Cochrane® databases using the keywords "diabetes", "diabetic retinopathy", "diabetic macular edema", "pathophysiology", "VEGF", "treatment", "anti-VEGF", "ranibizumab", "lucentis" with limitation of English language. The articles published between 2006–2016 years and we reviewed level I and level II studies.

Definition of level I studies are "high quality randomized trial or prospective study; testing of previously developed diagnostic criteria on consecutive patients; sensible costs and alternatives; values obtained from many studies with multiway sensitivity analyses; systematic review of Level I (RCT) and Level I studies" [9].

Level II studies are "less quality RCT; prospective comparative study; retrospective study; untreated controls from an RCT; less quality prospective study; development of diagnostic criteria on consecutive patients; sensible costs and alternatives; values obtained from limited studies; with multiway sensitivity analyses; systematic review of Level II studies or Level I studies with inconsistent results" [9].

RESULTS

Two anti-VEGF is approved for the DME treatment, ranibizumab (Lucentis˙; Genentech Inc., San Francisco, Calif., USA) and aflibercept (EYLEA˙; Regeneron, Tarrytown, N.Y., USA). Bevacizumab currently is not approved for diabetic macular edema but widely used as "off label".

Ranibizumab is a humanized monoclonal antibody that binds all biologically active isoforms and active proteolytic fragments of VEGF-A, therefore preventing VEGF-A to bind with its receptor. [10]

A pilot study of ranibizumab injection in 10 patients showed that ranibizumab is well tolerated, has potential to maintain or improve BCVA and reduce retinal thickness in patients with center-involved clinically significant DME [11].

Several level I studies such as Diabetic Retinopathy Clinical Network (DRCR.net), RESTORE Study, RISE and RIDE support the use of ranibizumab for DME patients. These studies reported that ranibizumab monotherapy or combination with laser give a better visual acuity outcomes at 1 to 2 years compared with laser or triamcinolone [12–15]. When comparing with other anti-VEGF (bevacizumab and aflibercept), one study (Protocol T) showed that in year 1 among eyes with worse baseline VA, aflibercept showed superiority over ranibizumab and bevacizumab but at year 2, the superiority over ranibizumab was no longer identified (Table 1) [16, 17].

In The Diabetic Retinopathy Clinical Research Network (DRCR.net) evaluation of intravitreal 0.5 mg ranibizumab or 4 mg triamcinolone combined with focal/grid laser compared with focal/grid laser monotherapy for treatment of diabetic macular edema were studied.

A total 854 study eyes were randomized of combination sham injection and prompt laser (n = 293), 0.5 mg ranibizumab and prompt laser (n = 187), 0.5 mg ranibizumab and deferred laser (n = 188), or 4 mg triamcinolone and prompt laser (n = 186). Prompt laser was given 3–10 days after injection while deferred laser was given ≥ 24 weeks, intravitreal study drug or sham injection retreatments every 4 weeks based on criteria in the protocol [12].

The 1-year mean change in the visual acuity letter score from baseline was significantly greater in the combination of ranibizumab and prompt laser group and ranibizumab and deferred laser group (both +9 letters and p < 0.05) but not in the combination of triamcinolone and prompt laser group (+4 letters, p = 0.31) compared with prompt laser monotherapy group (+3 letters). Conclusion of the 2-year expanded results are similar with to 1-year results that combination of ranibizumab with prompt or deferred laser is more effective compared with prompt laser monotherapy [12, 13].

The study extended to 5-year and from 3-year follow up, the objective is to evaluate prompt versus deferred (for ≥ 24 weeks) focal/grid laser treatment in eyes treated with intravitreal 0.5 mg ranibizumab. Five-year result suggest that focal/grid laser treatment at the initiation of ranibizumab is no better than deferred laser [18, 19].

Another level I, RESTORE Study, a multicenter, randomized, double-masked, laser-controlled phase III study. Three hundred forty five DME patients randomized into 3 groups, 0.5 mg ranibizumab + sham laser (n = 116), 0.5 mg ranibizumab + active laser (n = 118), or laser + sham injection (n = 111). Ranibizumab/sham injection was given 3 months then pro re nata (PRN); laser/sham laser was given at baseline then PRN [14].

In the 12 month report, ranibizumab monotherapy and combination with laser were superior to laser alone in improving mean change in BCVA from baseline to month 1 through month 12 (+6.1 and +5.9 vs. +0.8; both p < 0.0001). The mean cen-

Table 1. Randomized study results (Level I evidence) of ranibizumab in diabetic macular edema

Author(s), Year	Objective	Study Design	No. of Eyes or Patients	Outcome Measures	Treatment Regimen	Duration of Study	Results
DRCR.net, et al. 2010, 2011 [12,13]	IVT ranibizumab or triamcinolone combination with focal/grid laser vs with focal/grid laser monotherapy	Multicenter, randomized	854 eyes of 691 patients	BCVA and Safety	sham injection + prompt laser (n = 293), 0.5 mg ranibizumab + prompt laser (n = 187), 0.5 mg ranibizumab + deferred laser (n = 188), or 4 mg triamcinolone + prompt laser (n = 186) Prompt laser (within 3–10 days after IVT) Deferred laser (≥ 24 weeks after IVT)	2 years	1-year mean change in VA from baseline: ranibizumab + prompt laser group and ranibizumab + deferred laser group (both +9 letters, $p < 0.001$); triamcinolone + prompt laser group (+4 letters, $p = 0.31$) compared with the sham + prompt laser group (+3 letters) At 2-year, compared with sham + prompt laser group, mean change in VA from baseline was greater in ranibizumab + prompt laser group (+3.7 letters) and in ranibizumab + deferred laser group (+5.8 letters); 1.5 worsen in triamcinolone combination with prompt laser group (-1.5 letters) No systemic events difference between study treatment. Endophthalmitis related with injection were 0.8% in ranibizumab groups. Elevated intraocular pressure and cataract surgery more frequent in the triamcinolone + prompt laser group
Mitchell P, et al. 2011 (RESTORE) [14]	IVT ranibizumab monotherapy or combined with laser over laser alone	Multicenter, randomized, double-masked, laser-controlled	345 patients	BCVA	IVT ranibizumab + sham laser (n = 116), IVT ranibizumab+ laser (n=118), or sham injections + laser (n = 111) IVT ranibizumab/sham injection: 3 initial consecutive monthly then prn	12 months	Mean change BCVA from baseline to month 1 through month 12 (+6.1 and +5.9 vs. +0.8; both $P < 0.0001$)
Nguyen QD, et al. 2012 (RISE and RIDE) [15]	IVT ranibizumab	Multicenter, double-masked, sham injection-controlled, randomized	RISE = 377 patients / RIDE = 382 patients	BCVA	IVT ranibizumab (0.5 or 0.3 mg) or sham injections All monthly injection and with rescue laser per protocol criteria	24 months	In RISE, 18.1% of sham patients gained ≥ 3 lines vs 44.8% of 0.3 mg and 39.2% of 0.5 mg ranibizumab (both $p < 0.05$) In RIDE, 12.3% of sham patients gained ≥ 3 lines vs. 33.6% of 0.3 mg patients and 45.7% of 0.5 mg ranibizumab (both $p < 0.0001$)

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Author(s), Year	Objective	Study Design	No. of Eyes or Patients	Outcome Measures	Treatment Regimen	Duration of Study	Results
DRCR.net, 2015 [16] and Wells JA, et al. 2016 [17]	IVT aflibercept, bevacizumab and ranibizumab	Multicenter, randomized	660 patients	VA at year 1 and 2, adverse event and retreatment frequency at year 2	IVT Aflibercept 2.0 mg (n = 224), bevacizumab 1.25 mg (n = 218), or ranibizumab 0.3 mg (n = 218)	2 years	Mean VA improvement from baseline to 1 year were 13.3 with aflibercept, 9.7 with bevacizumab, and 11.2 with ranibizumab (p < 0.05 for aflibercept vs. bevacizumab and for aflibercept Vs. ranibizumab) At year-2, mean VA improved by +12.8 for aflibercept, +10.0 for bevacizumab, and +12.3 letters for ranibizumab APTC events occurred higher in ranibizumab (12%) compared with aflibercept (5%) or bevacizumab (8%) Median numbers of injections for aflibercept, bevacizumab, and ranibizumab were 5, 6, and 6 in year 2, respectively

DRCR.net — diabetic research clinical research network; IVT — intravitreal injection; DME — diabetic macular edema; CRT — central retinal thickness; BCVA — best corrected visual acuity; VA — visual acuity; prn — pro re nata; APTC — Anti-Platelet Trialists' Collaboration

tral retinal thickness was significantly reduced from baseline with ranibizumab monotherapy (-118.7 μm) and ranibizumab + laser combination (-128.3 μm) versus laser monotherapy (-61.3 μm; both p < 0.001) [14].

All patients eligible to receive 0.5 mg ranibizumab PRN from month 12 in RESTORE study included in extension study. Overall, 208 patients completed the extension study. Individualized ranibizumab treatment during the extension study could maintain the BCVA and central retinal thickness (CRT) observed at month 12 over the 2-year extension study (+8.0 letters, -142.1 μm [prior ranibizumab] and +6.7 letters, -145.9 μm [prior ranibizumab + laser] from baseline at month 36). Mean injection of 6.8 injections in prior ranibizumab group and 6.0 injections in prior ranibizumab + laser group. No new safety concern in ranibizumab group were identified [20, 21].

Two parallel, methodologically identical, phase III, multicenter, double-masked, sham injection–controlled, randomized studies, RISE and RIDE. Ranibizumab was given monthly and in the third year, eligible patients sham patients cross-over to 0.5 mg ranibizumab while still masked [15].

In RISE, 377 patients were randomized (sham n = 127, 0.3 mg ranibizumab n = 125, 0.5 mg ranibizumab n = 125).17,18 At 24 months, 18.1% of sham patients gained ≥ 3 lines versus 44.8% of 0.3 mg and 39.2% of 0.5 mg ranibizumab patients (both p < 0.05) [15].

Visual acuity (VA) outcomes in ranibizumab group were consistent from month 24 through through month 36. Proportions of patients who gained ≥ 3 lines from baseline at month 36 in the sham/0.5 mg, 0.3 mg, and 0.5 mg ranibizumab groups were 22.0%, 51.2%, and 41.6%, respectively [22].

In RIDE, 382 patients were randomized (sham n = 130, 0.3 mg n = 125, 0.5 mg n = 127). At 24 months, ranibizumab-treated patients gained ≥ 3 lines: 12.3% of sham patients versus 33.6% of 0.3-mg and 45.7% of 0.5-mg ranibizumab (both p < 0.0001) [15].

Visual acuity (VA) outcomes in ranibizumab group were consistent at month 24 through month 36. Proportions of patients who gained ≥ 3 lines from baseline at month 36 in the sham/0.5 mg, 0.3 mg, and 0.5 mg ranibizumab groups were 19.2%, 36.8%, and 40.2%, respectively [22].

A "head to head" study, multicenter trial comparing ranibizumab, repackage bevacizumab, and

Table 2. Randomized study results (Level II evidence) of ranibizumab for diabetic macular edema

Author(s), Year	Objective	Study Design	No. of Eyes or Patients	Outcomes Measures	Treatment Regimen	Duration of Study	Results
Nguyen QD, et al. 2009 (READ-2) [23]	IVT ranibizumab vs focal/grid laser vs. combination	Prospective, randomized, interventional, multicenter	126 patients	BCVA	Group 1: 0.5 mg of ranibizumab at baseline, months 1, 3, and 5 (n = 42); Group 2: focal/grid laser photocoagulation at baseline and month 3 prn (n = 42); Group 3: a combination of 0.5 mg of ranibizumab and focal/grid laser at baseline and month 3 (n = 42)	6 months	Mean BCVA was significantly greater in group 1 vs group 2 (+7.24 letters vs -0.43 letters; p=0.01); group 3 (+3.8 letters) not statistically different from the 2 groups
Massin P, 2010 (RE-SOLVE) [25]	IVT ranibizumab	Multicenter, sham controlled, double-masked study	151 patients	CRT and BCVA	IVT Ranibizumab (0.3 mg or 0.5 mg; n = 51 each) or sham (n = 49)	12 months	Improvement of BCVA at month 12 from baseline were +10.3 letters in ranibizumab and —1.4 letters in sham (p < 0.0001) Mean CRT reduction were —194.2 μm in ranibizumab and —48.4 μm in sham (p < 0.0001)

IVT — intravitreal injection; DME — diabetic macular edema; CRT — central retinal thickness; BCVA — best corrected visual acuity; prn — pro re nata

aflibercept in United States. Six hundred and sixty adults with DME was randomized to receive intravitreal injection 2.0 mg aflibercept (n = 224), 1.25 mg bevacizumab (n = 218), or 0.3 ranibizumab (n = 218) every 4 weeks based on criteria in the protocol. If DME persisted after 6 months, focal/grid laser photocoagulation could be added [16, 17].

Improvement in mean VA from baseline to 1 year were 13.3 letters with aflibercept, 9.7 letters with bevacizumab, and 11.2 letters with ranibizumab. The difference in the improvement between 3 anti-VEGF was not clinically meaningful because it was driven by the eyes with worse visual acuity at baseline (p < 0.001 for interaction) [16].

When the baseline of visual acuity was 78 to 69 letters (equivalent to approximately 20/32 to 20/40) (51% participants), the mean improvement was 8.0 letters with aflibercept, 7.5 letters with bevacizumab, and 8.3 letters with ranibizumab (p > 0.50 for each pairwise comparison).

There were no significant differences among the study groups in the rates of serious adverse events [16].

In 2-year, median number of injection for aflibercept, bevacizumab, and ranibizumab were 5, 6, and 6, respectively. While the median number over 2 years were 15, 16, and 15 in the aflibercept, bevacizumab, and ranibizumab groups, respectively. Forty one percent in aflibercept groups, 64% in bevacizumab group, and 52% in ranibizumab groups was administered focal/grid laser photocoagulation (aflibercept vs either ranibizumab or bevacizumab and bevacizumab vs ranibizumab all p < 0.05) [17].

Mean VA improvement at 2 years were 12.8, 10.0, and 12.3 letters in aflibercept, bevacizumab, and ranibizumab respectively. The study concluded not only aflibercept, bevacizumab, and ranibizumab showed VA improvement from baseline to 2 years but also a decreased number of injections in year 2. Aflibercept had superior VA outcome compared with bevacizumab in 2-year but the superiority compared with ranibizumab that is shown in year 1 is no longer shown in year 2 [17].

The regimen used in the "head to head" trials is not reflected the clinical practice in Indonesia where ranibizumab available and approved by Indonesian health authority is 0.5 mg.

RESOLVE and READ-2 studies are 2 level II studies reported ranibizumab monotherapy or combination improved BCVA until 1 to 2 years compared with no treatment or with laser [23-25]. One

level II study, READ-2, showed the mean decrease of CRT is significant compared sham patients. [25]

READ-2 conducted in multicenter, 126 DME patients randomized into three groups. Group 1 receive 0.5 ranibizumab at baseline, month 1, month 3, and month 5 (n = 42); group 2 received focal/grid laser photocoagulation at baseline and month 3 pro re nata (n = 42), or group 3 is combination of 0.5 mg ranibizumab and focal/grid laser at baseline and month 3 (n = 42) [12, 13].

The primary endpoint month 6, the mean change of BCVA was significantly greater in group 1 compared with group 2 (+7.2 vs. -0.43 letters, p = 0.01), and group 3 (+3.8 letters) was not statistically different from the other 2 groups. Improvement of ≥ 3 lines occurred in 22% group 1, 0% in group 2 (p = 0.002), and 8% in group 3 [24].

After 6 months, most patients were continued with ranibizumab, 33 patients in group 1, 34 patients in group 2, and 34 patients in group 3 remained in the study through 24 months, with mean improvement in BCVA 7.7, 5.1, and 6.8 letters at month 24. Patients who gained ≥ 3 lines was 24%, 18%, and 26% at month 24 [24].

In RESOLVE study, phase II clinical trial, 151 patients was randomized to ranibizumab 0.3 mg (n = 51), ranibizumab 0.5 mg (n = 51), or sham treatment (n = 49) three monthly injection. Thereafter, treatment could be stopped or reinitiated with an opportunity for rescue laser photocoagulation (based on protocol). After month 1, the ranibizumab dosage (or sham) could be doubled to 0.6 mg (for ranibizumab 0.3 mg) and 1.0 mg (for ranibizumab 0.5 mg) if met indicated by specific study criteria.

At month 12, BCVA improvement from baseline were +10.3 letters in ranibizumab group and decline in sham group by -1.4 letters (p < 0.0001). Mean CRT reduction is -194.2 μm with ranibizumab and -48.4 μm with sham (p < 0.0001). In ranibizumab group, 60.8% gain ≥ 10 letters from baseline and 18.4% in sham group (p < 0.0001) [25].

CONCLUSIONS

Review from several level I and level II intravitreal ranibizumab injection studies suggests that ranibizumab alone and/or combination with laser is safe and effective for DME patients for over 2 years treatment.

Comparison with other anti-VEGF also suggest that ranibizumab is effective for DME patients for

over 2 years treatment. Future research on the safety and effective ranibizumab 0.5 mg compared with other anti-VEGF is required.

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Conflict of interest:

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