A Review of Efficacy and Safety of Anti-Vascular Endothelial Growth Factor (Anti-VEGF) Therapies Compared to Conventional Treatment in Patients with Retinal Vein Occlusion (RVO)

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Abstract

Anti-VEGF therapies, which are mainly used in cancer treatment, are now being used for the treatment of retinal vein occlusion (RVO). With diabetes being the major risk factor for developing RVO, which can cause permanent blindness. This systematic review was undertaken to assess the efficacy and safety of newer Anti-VEGF therapy compared to conventional laser photocoagulation and intra-vitreal steroid therapy for RVO, from the data reported in randomized controlled clinical trials (RCTs). A search for relevant studies was conducted in the Cochrane Library, ClinicalTrials.gov, MEDLINE, PubMed, and Web of Science using the search term. "Retinal vein occlusion AND (anti VEGF OR ranibizumab OR bevacizumab OR aflibercept OR Lucentis OR Avastin OR VEGF trap OR eylea) AND (laser OR corticosteroid OR dexamethasone OR triamcinolone)". Out of the initial 2,236 trials, 12 were chosen to be reviewed according to inclusion and exclusion criteria. Anti-VEGF reports better visual acuity outcomes compared to intra-vitreal corticosteroids and laser photocoagulation. It also showed a greater reduction in CRT than other therapeutic options. Anti-VEGF's safety profile was comparable to other therapies. Anti-VEGF drugs show better efficacy in patients with RVO as compared to conventional treatments. Nevertheless, the long-term safety and treatment cost need to be considered while prescribing the treatment.*

Keywords: *Diabetes mellitus; Intra-vitreal corticosteroids; Laser photocoagulation; BRVO; CRVO*

INTRODUCTION

Retinal vein occlusion (RVO) occurs following diabetic retinopathy and can lead to decreased visual acuity and permanent blindness (Klein *et al.*, 2008). RVO has a higher prevalence in type 2 diabetes due to decreased ocular perfusion; therefore, eye examinations are mandatory for type 2 diabetics (Cho *et al.*, 2019; WHO, 2018). RVO is caused by venous occlusion due to a clot, vessel pathology, or external compression to the veins of the retina (Zhou *et al.*, 2013; Kolar, 2014). Depending on the part of the retinal vein occluded, RVO can be divided into central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) (Kolar, 2014; Hayreh, 2014). Due to RVO, there can be interstitial fluid leakage leading to the release of various cytokines like vascular endothelial growth factors (VEGF), which can induce endothelial cell growth leading to macular oedema (Qian *et al.*, 2018). Vision loss in RVO occurs due to macular oedema or macular ischemia (Hayreh, 2014; Braithwaite *et al.*, 2014).

There are various treatment therapies available for the treatment of RVO. Laser photocoagulation has been the standard of care for treatment of RVO for the last few decades (Rehak and Rehak, 2008). Steroidal intra-vitreal injections and implants have been approved for RVO treatment in the last decade, due to their anti-inflammatory effects on reducing oedema (Holz *et al.*, 2013; Schmucker *et al.*, 2012). Anti-vascular endothelial growth factors (Anti-VEGF) have previously been used to treat cancers, have now been developed for intra-vitreal use (Qian *et al.*, 2018). These anti-VEGF include Ranibizumab, which is a humanized recombinant monoclonal antibody that binds with vascular endothelial growth factors (VEGF) and this in turn prevents binding of these VEGF to their corresponding receptors (Pielen *et al.*, 2013; Brown *et al.*, 2011).

Most systematic reviews in this area compare either different anti-VEGF drugs with each other (Schmucker *et al.*, 2011) or

an anti-VEGF drug with a steroid (Qian *et al.*, 2018; Pielen *et al.*, 2013). This systematic review was undertaken to assess the efficacy and safety of newer anti-VEGF therapy compared to conventional laser photocoagulation and intra-vitreal steroid therapy for RVO, from the data reported in randomized controlled clinical trials (RCTs).

MATERIALS AND METHODS

Literature Search

A systematic search was performed on 20 June 2020 using the search term "retinal vein occlusion AND (anti VEGF OR ranibizumab OR bevacizumab OR aflibercept OR Lucentis OR Avastin OR VEGF trap OR eylea) AND (laser OR corticosteroid* OR dexamethasone OR triamcinolone)" in Cochrane Library, ClinicalTrail.gov, MEDLINE, PubMed, and Web of Science. No filter restrictions were applied.

Inclusion and Exclusion Criteria

The inclusion criteria were parallel design RCTs that compared anti-VEGF with either laser photocoagulation or intra-vitreal steroid treatment only, in patients with RVO with

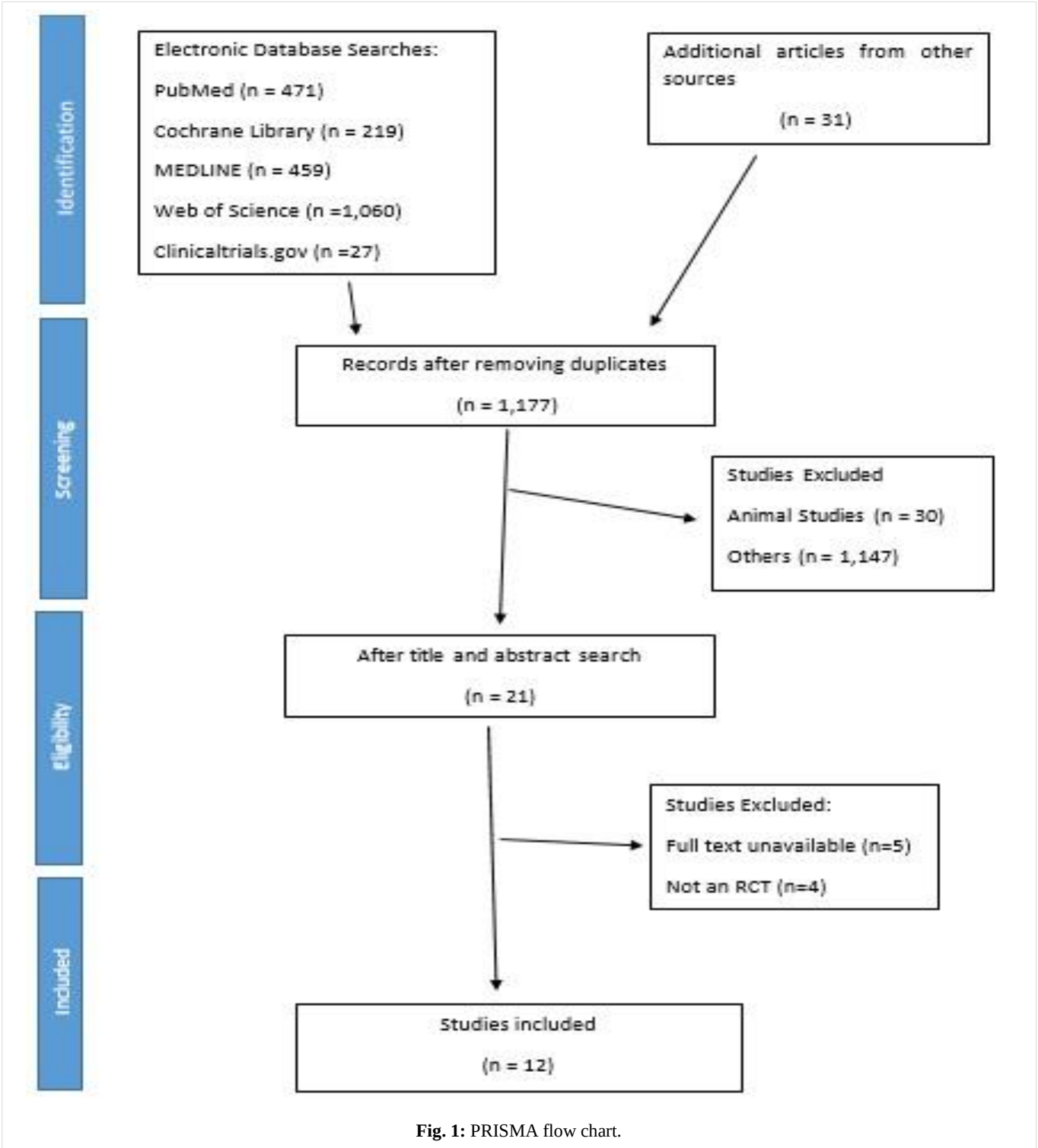

Fig. 1: PRISMA flow chart.

at least 3 months of follow-up and assessed at least two of the outcomes mentioned below. Only articles with free full-text availability and in English were included. Unpublished studies were considered if they met the inclusion criteria. Animal studies, meeting abstracts, case reports, case series, and review articles were excluded.

Outcomes

The outcomes assessed were change in best-corrected visual acuity (BCVA) from baseline, reported in ERDTS letters, in the study eye, and change in central retinal thickness (CRT) from baseline in the study eye, reported in microns, as the efficacy outcomes and ocular and non-ocular adverse events.

Data Extraction

A single researcher carried out the screening and data extraction process. Data extraction comprised the following data: total number of patients, number of treated patients in each group, control treatment, follow-up time, baseline visual acuity, mean change in visual acuity from baseline to follow-up period, baseline CRT, change in central retinal thickness from baseline in the study eye, and baseline and. Where the duration was given in weeks or days, it was transformed to mean time in months and baseline and change in intraocular pressure (IOP) in the study eye, where the duration was given in weeks or days, it was transformed to mean time in months. Visual acuity is given in number of letters (according to ETDRS scores) and was changed to letters if reported in log MAR. For safety assessment, the information was extracted on the percentage (and/or number of patients) of conjunctival haemorrhage, eye pain, vitreous haemorrhage, and other ocular adverse events. Regarding systemic adverse events, the information was extracted on the incidence of hypertension, nasopharingitis, and other events, including myocardial infarction, cerebrovascular accidents, and infection.

Assessment of Bias

The risk of bias was assessed by using the JADED score (Jadad *et al.*, 1996). It is a questionnaire to assess the randomization, blinding, and patient reporting, by giving each study a score out of five, with five being least biased.

RESULTS

The study selection procedure is illustrated as a PRISMA flow chart in Fig. 1. 2,236 trials were identified by the electronic literature search of five databases, namely Cochrane Library, ClinicalTrials.gov, Medline, PubMed, and Web of Science, by using the search terms mentioned above. After removing duplicates, 1,177 trials remained, and only 21 remained after reviewing titles and abstracts. Of these 21, five were excluded due to the fact that no free full-text was available (Mylonas *et al.*, 2020; Russo *et al.*, 2009; Campochiaro *et al.*, 2013; Cao *et al.*, 2019; Guignier *et al.*,

Table 1: Characteristics of various studies under review.

Study / Author	Location	Participants (Male/Female)	Intervention				Duration (months)	Patient Population	Mean	JADED Score
			Anti-VEFG	Steroid	Laser	Combination / Sham				
BRIGHTER	Multicentre (Europe, Australia, Canada)	455 (226/229)	183		92	180	24	ME, BRVO	63.3 ± 10.30	3
COMO	Multicentre (Europe)	307 (179/128)	153	154			12	ME, BRVO	67 ± 11.4	2
COMRADE - B	Multicentre (Europe)	244 (111/133)	126	118			6	ME, BRVO	65.6 ± 10.5	3
COMRADE - C	Multicentre (Europe)	234 (145/98)	124	119			6	ME, BRVO	66.1 ± 11.9	4
Higashiyama, 2013	Singlecenter (Japan)	43 (17/26)	22	21			12	ME, BRVO	68.45 ± 9.4	4
NCT, 2011	Multicentre (Europe)	307 (179/128)	153	154			12	BRVO	67.0 ± 11.41	3
NCT, 2012	Multicentre (USA, Canada, Japan)	183 (98/83)	191		90		6	ME, BRVO	65.5 ± 10.98	4
Lucatto, 2017	Singlecenter (USA)	35 (22/13)	14	11		10	6	ME, CRVO	59.48 ± 13.22	5
RABAMES	Multicentre (Europe)	30 (15/15)	10		10	10	6	ME, BRVO	66.3 ± 9.77	4
Ramezani, 2012	Singlecenter (Iran)	86 (44/42)	43	43			6	BRVO	59 ± 8	5
VISTA DME	Multicentre (USA)	466 (251/210)	307		154		24	DME, CRVO	62.2 ± 9.7	4
VIVI DME	Multicentre (Europe, Australia, Japan, Taiwan)	404 (250/154)	271	133			24	DME, CRVO	63.6 ± 8.3	4

ME – Maculae oedema; BRVO – Branch retinal vein occlusion; CRVO – Central retinal vein occlusion; DME – Diabetic macular oedema

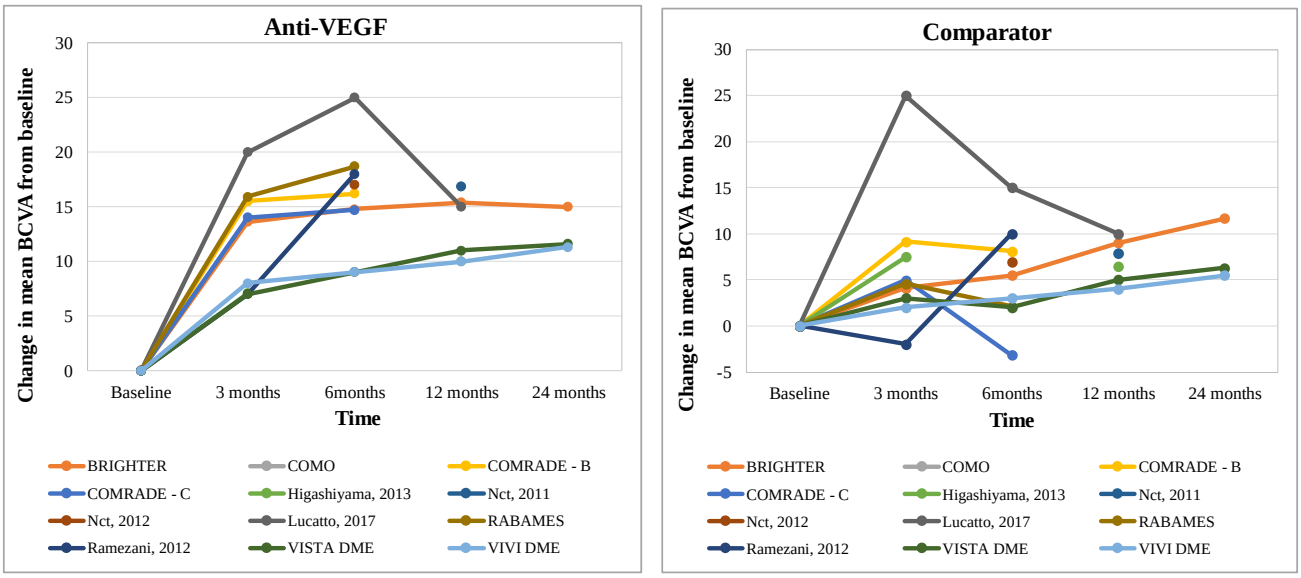

Fig. 2: Graphs depicting change in best-corrected visual acuity (BCVA) from baseline in anti-VEGF and comparator groups

2013), and four were excluded as the trial methodology was not a randomized controlled trial (Yumusak *et al.*, 2015; Kaldrm and Yazgan, 2018; Chatziralli *et al.*, 2017). Thus, 12 RCTs were included in the final systematic review (Hattenbach *et al.*, 2018; Brown *et al.*, 2015; Lucatto *et al.*, 2017; Higashiyama *et al.*, 2013; Regeneron Pharmaceuticals, 2011; Ramezani *et al.*, 2012; Pielen *et al.*, 2015; NCT01396083, 2011; Bandello, *et al.*, 2018; NCT01521559, 2014; Tadayoni *et al.*, 2017).

Study Characteristics

The basic characteristics of the 12 randomized controlled trials are presented in Table 1. Four RCTs compared Anti-VEGF versus laser photocoagulation, and eight RCTs compared Anti-VEGF versus steroid injections or implants. The sample size ranges from 30 to 466 participants, with 10 minimum participants in each intervention group. The combination therapy intervention group and the sham injections group were excluded when reporting results data. All twelve of the studies reported results for BCVA, CRT, and ocular and non-ocular adverse events.

BCVA

Of all the studies, three reported BCVA in Log MAR (Higashiyama *et al.*, 2013; NCT01521559, 2014; Tadayoni *et al.*, 2017), which was converted into ETDRS letters for presenting results. The BCVA was reported at three, six, twelve, and twenty-four months (Fig. 2). The gain in letters indicates improvement in visual acuity of the patient. The baseline BCVA ranged from 46 letters to 70 letters in ETDRS visual acuity testing charts in both the comparator group and anti-VEGF group across all studies.

At three months, the anti-VEGF group reported a gain of letters ranging from 7 to 20 letters compared to the comparator group that reported a loss of 2 letters to a gain of a maximum of 25 letters. At six months, anti-VEGF reported a gain ranging from 9 to 25 letters, while the comparator group reported a loss of 3 letters to a gain of a maximum of 15 letters. At twelve months, the anti-VEGF group reported a gain of letters ranging from 10 to 17 letters compared to the comparator group, which reported a gain of 4 to 10 letters. At the end of twenty-four months, the anti-VEGF group reported a gain ranging from 11 to 15 letters, while the comparator group reported a gain ranging from 5 to 12 letters.

For calculating the weighted mean, the following formula was used:

$$\overline{w} = \frac{\sum_{i=1}^{k} w_i n_i}{\sum_{i=1}^{k} w_i}$$

where ‘n’ is the number of patients in the group in all twelve studies (k), and ‘w’ is the mean change in BCVA from baseline.

CRT

The retinal thickness was reported in microns in all the studies and represents the anatomical changes in the fovea following treatment. The CRT was reported at three, six, twelve, and twenty-four months (Fig. 3). The baseline CRT ranged from 370 to 870 microns in both the Anti-VEGF and comparator groups.

At three months, CRT reduction ranged from 60 to 380 microns in the anti-VEGF group, while the comparator group showed a reduction from 40 to 295 microns on average. At six months, the anti-VEGF group reported a CRT reduction from 103 to 406 microns, while the comparator group reported a CRT reduction from 50 to 438 microns. At twelve months, CRT reduction ranged from 210 to 316 microns in the anti-VEGF group, and the comparator group reported a reduction from 66 to 438 microns. At the end of twenty-four months, the anti-VEGF group reported a CRT reduction from 191 to 220 microns while the comparator group reported a CRT reduction from 84 to 107 microns.

Adverse Events

The adverse events reported in all twelve studies, which

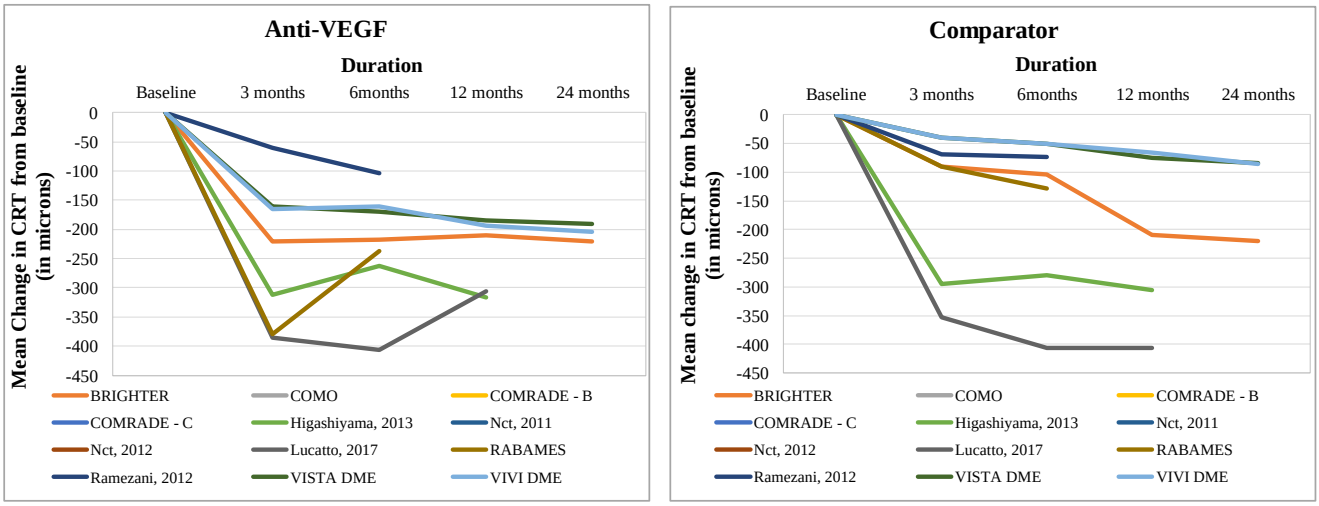

Fig. 3: Graphs depicting change in central retinal thickness (CRT) from baseline in anti-VEGF and comparator groups

Table 2: Adverse events (AEs) reported.

Study	Total Ocular AEs		Total Non-Ocular (Systemic) AEs	
	Anti-VEGF	Comparator	Anti-VEGF	Comparator
BRIGHTER	87	7	116	35
COMO	80	187	127	104
COMRADE - B	71	89	79	98
COMRADE - C	77	99	124	119
Higashiyama, 2013	2	5	*NR*	*NR*
NCT, 2011	64	147	40	28
NCT, 2012	34	22	40	50
Lucatto, 2017	17	17	*NR*	*NR*
RABAMES	0	0	1	0
Ramezani, 2012	1	17	*NR*	*NR*
VISTA DME	307	154	307	154
VIVI DME	171	133	123	51
NR – data not reported in the study				

comprised of 2,794 patients, are shown in Table 2. The most common adverse events reported were eye pain, conjunctival haemorrhage, and nasopharyngitis.

DISCUSSION

Twelve studies were analysed on efficacy of anti-VEGF compared to conventional, intra-vitreal steroidal injections/implants and photocoagulation. Laser photocoagulation reported the least gain in letters, while anti-VEGF showed the most gain in letters. The effect of intra-vitreal steroids on visual acuity varied greatly. The variation could be due to pulsatile administration of corticosteroids, high concentration in the early phase followed by a lower concentration period (Chang-Lin *et al.*, 2011). The gain in visual acuity improved over time in most instances. The most gain in visual acuity is seen up to six months and stalls after six months. This is consistent with other systematic reviews comparing anti-VEGF with intra-vitreal corticosteroids (Qian *et al.*, 2018; Ji *et al.*, 2019).

CRT is defined as the distance between the internal membrane and the inner surface of the retinal epithelium. It is measured manually at the fovea and is considered as an anatomical measure of ME. The standard of deviation for CRT over 100 microns across all the studies (Hattenbach *et al.*, 2018; Brown *et al.*, 2015; Lucatto *et al.*, 2017; Higashiyama *et al.*, 2013; Regeneron Pharmaceuticals, 2011; Ramezani *et al.*, 2012; Pielen *et al.*, 2015; NCT01396083, 2011; Bandello *et al.*, 2018; NCT01521559, 2014; Tadayoni *et al.*, 2017). Reduction in CRT followed the same trend as improvement in visual acuity. Anti-VEGF showed the most improvement, similar to another systematic review of six-month data (Qian *et al.*, 2018). The result is contrary to another review that reported more reduction in CRT with laser photocoagulation than anti-VEGF (Yong *et al.*, 2015).

Various ocular adverse events were reported in the studies, with the most common being raised IOP, conjunctival and vitreal haemorrhage, as well as cataract. These ocular adverse events are similar to those reported in other studies and reviews (Qian *et al.*, 2018; Ji *et al.*, 2019; Eter *et al.*, 2017). High incidence of adverse events was reported in studies where raw data were reported as compared to published studies. Bevacizumab, even in the lowest approved dose, has been associated with the risk of impairment of cardiac function (Fogil *et al.*, 2018; Chen and Ai, 2016). Additionally, cataract incidence is associated with injection frequency, as corticosteroids require fewer number of injections, thus less incidence of cataract (Qian *et al.*, 2018). Similar to the results in the studies. However, ranibizumab is associated with lowered instances of raised IOP (Qian *et al.*, 2018; Gu *et al.*, 2017), similar to results reported in the reviewed studies. Laser photocoagulation has more severe vision-impairing adverse events than anti-VEGF (Yong *et al.*, 2015; Hirami *et al.*, 2007), similar to the data reported in the revised studies. In view of this, patients' IOP should be kept in mind when deciding which treatment option should be chosen, as anti-VEGF and intra-vitreal corticosteroids both show almost comparable improvement in visual acuity.

For the cost burden of treatment, corticosteroids are more cost effective than anti-VEGF (Ji *et al.*, 2019; Li *et al.*, 2018). This is possibly because intra-viteral corticosteroids require less number of injections as compared to anti-VEGF.

Limitations

There were several limitations of the studies included in the review. Firstly, three of the RCTs had a small sample size. Secondly, four studies did not report the method of randomization used, which could be a possible source of bias. Thirdly, heterogeneity was present between the studies due to the different anti-VEGF and corticosteroid therapies used in the studies. Lastly, pharmaceutical companies funded most of the anti-VEGF studies, which could be a potential source of bias towards anti-VEGF.

The systematic review itself has some limitations. Firstly, only one assessor conducted the review, which could potentially be a source of inclusion bias. In addition, only studies in the English language and free full-text available studies were eligible for review. As a result, it might be a source of sampling bias in the review.

CONCLUSION

This review showed that anti-VEGF reports better visual acuity outcomes compared to intra-vitreal corticosteroids and laser photocoagulation. Anti-VEGF also showed greater reduction in CRT than other therapeutic options. All three of the therapeutic options showed improvement in both visual acuity and retinal thickness over time, but it peaks at six months. Both ocular and systemic adverse events are observed in all three of the therapies. Anti-VEGF and intra-vitreal steroids have a comparable safety profile. While laser photocoagulation reports more incidences of severe ocular adverse events that can cause visual impairment. In addition, patients' IOP should be checked while administering intra-vitreal corticosteroid.

More RCTs need to be done that report the long-term efficacy and safety outcomes beyond six months. As these can provide further evidence as to whether or not the improvement in visual acuity peaks at 6 months and provide data on the long-term safety profile of anti-VEGF drugs.

In conclusion, anti-VEGF drugs show better efficacy in patients with RVO as compared to conventional treatments. Nevertheless, the long-term safety and treatment cost need to be considered while prescribing the treatment.

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The present research did not receive any financial support.

Conflict of Interest

The author declares that there is not any conflict of interest regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/ or falsification, double publication and/or submission, and redundancy, have been completely observed by the author.

Life Science Reporting

No life science threat was practiced in this research.

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