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Therapeutic effects of various therapeutic strategies on non-exudative age-related macular degeneration

A PRISMA-compliant network meta-analysis of randomized controlled trials

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Abstract

Purpose: Age-related macular degeneration (AMD) is a chronic progressive central retinal disease. Geographic atrophy (GA) is a late stage of dry AMD (DAMD) and is a slowly but inexorably progressive disease that causes irreversible blindness over time. We aimed to assess various therapeutic strategies for DAMD and GA treatment by network meta-analysis.

Methods: We searched PubMed, Embase, and the Cochrane Library to identify randomized controlled trials (RCTs) of atrophic AMD treatments published prior to December 16, 2017. Best-corrected visual acuity (BCVA) and change in GA area were evaluated to reflect therapeutic effects. A random-effects network meta-analysis, with a frequentist framework, was used to assess the effectiveness of therapeutic strategies for DAMD treatment.

Results: We included 22 articles that assessed 16 types of regimens and 2482 patients in our meta-analysis. The network meta-analysis results showed that zinc-monocysteine (98.1%) was the most likely to improve BCVA (logMAR), followed by alprostadil (84.0%), eculizumab (70.5%), and rheohemapheresis (67.3%). In BCVA (letters) outcomes, rheohemapheresis (99.6%), lampalizumab (69.5%), and the antioxidant complex (67.9%) showed marked benefits in visual function recovery. Regarding the outcome of GA area change, isopropyl unoprostone (IU) (88.6%) might have the best GA area reduction; however, there was no significant difference between IU and the blank control.

Conclusions: Zinc-monocysteine and rheohemapheresis showed significantly better effects on BCVA (logMAR) improvement, and compared with the blank control, rheohemapheresis and the antioxidant complex showed better effects on BCVA (letters) improvement. Other treatments have potential effects on DAMD, including alprostadil, eculizumab, and lampalizumab. However, there is no effective treatment for GA area reduction.

Abbreviations: ABMSC = autologous bone-marrow stem cells, AMD = age-related macular degeneration, BCVA = best-corrected visual acuity, CIs = confidence intervals, CLVQOL = Chinese-Version Low Vision Quality of Life, CNV = choroidal neovascularization, DAMD = dry age-related macular degeneration, GA = geographic atrophy, PRISMA-NMA = Preferred Reporting Items for Systematic Review and Meta-Analysis for Network Meta-Analysis, RCTs = randomized controlled trials, RPE = retinal pigment epithelium, SMDs = standard mean difference, SUCRA = surface under the cumulative ranking curve, VFQ = Visual Function Questionnaire.

Keywords: age-related macular degeneration, best-corrected visual acuity, geographic atrophy, meta-analysis

1. Introduction

Age-related macular degeneration (AMD) is a chronic progressive central retinal disease. The prevalence of any age-related macular degeneration is approximately 8.69% globally and is higher in Europe, at 12.3%.[1] At present, AMD is a major cause of vision loss worldwide.[2] In 2015, there were 8.4 million patients with moderate to severe vision impairment caused by AMD.[3] AMD is classified as dry AMD (DAMD) or neovascular AMD depending on the presence of choroidal neovascularization (CNV). In geographic atrophy (GA), a late stage of DAMD, progressive atrophy of the retinal pigment epithelium (RPE), choriocapillaris, and photoreceptors occur.[4] The risk factors for this late-stage AMD include increasing age, cigarette smoking, previous cataract surgery, and family history. Cardiovascular risk factors are also associated with late-stage AMD.[5]

Unlike neovascular AMD in which anti-angiogenic treatment leads to improvements in visual acuity, GA is characterized by progressive and irreversible loss of retinal cells that leads to loss of

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visual function.[6] Currently, there is no effective treatment for GA that can repair the RPE and outer retinal layers. However, multiple pathways, such as inflammation, oxidative stress, neuroprotection, complement activation, and blood flow regulation, have been implicated in the progression of DAMD.[4,7] New therapies for these related pathways are under investigation. In addition, new non-invasive inspection methods have provided evaluation tools for clinical research.[8] At present, the existing therapeutic methods for GA still need to be evaluated to determine which is more advantageous using direct and indirect comparisons. Therefore, this study first comprehensively analyzed various therapeutic strategies for DAMD treatment by network meta-analysis, which provides reference evidence for clinical applications.

2. Methods

We performed this meta-analysis according to the Preferred Reporting Items for Systematic Review and Meta-Analysis for Network Meta-Analysis (PRISMA-NMA) guidelines.[9] Our study was performed on the basis of previous studies; therefore, ethical approval and informed consent were not required.

2.1. Search strategy and selection criteria (http://links.lww.com/MD/C256)

A systematic literature search by 2 investigators was conducted in PubMed, Embase, and the Cochrane Library to identify randomized controlled trials (RCTs) published prior to December 16, 2017. The following search keywords were used: "dry," "nonexudative," "atrophic," "geographic atrophy," "age-related macular degeneration," and "random." The bibliographies of the obtained publications and relevant reviews were also assessed to ensure that no relevant studies were inadvertently omitted. The included criteria were as follows: RCT design; the subjects were atrophic AMD patients; all of the DAMD treatments were included; and the outcome assessment included best-corrected visual acuity (BCVA) and GA area change.

The excluded criteria consisted of the following: non-RCT design; not including DAMD patients; non-ophthalmic therapeutic studies, such as interventions to improve AMD patients' depressive symptoms; and irrelevant outcomes for this review defined as BCVA and GA area change. In addition, reviews, comments, academic dissertations, and other unrelated studies were excluded.

2.2. Data extraction and quality assessment

Two authors independently extracted the following information from the eligible studies: first author's name, publication year, register ID, sample size, age, ratio of gender, experimental intervention, control, and follow-up. We assessed the methodological quality of the included studies using the Cochrane Collaboration's tool, which assigns grades of "high," "unclear," and "low" risk of bias across seven specified domains, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.[10] This study evaluated 2 outcomes; the first was improvement in BCVA, determined by evaluation of visual function after treatment, and the second was change in GA area, which objectively reflected the therapeutic effect for GA.

2.3. Statistical analysis

We used a random-effects network meta-analysis, with a frequentist framework, for mixed multiple treatment comparisons because it allowed us to fully preserve the within-trial randomized treatment comparisons in each trial.[11] Network plots were produced for each outcome in which nodes were weighted according to the number of studies evaluating each treatment and edges according to the precision of the direct estimate for each pair wise comparison. Inconsistency between direct and indirect sources of evidence was globally assessed by comparing the fit and parsimony of consistency and inconsistency models and was locally assessed by calculating the differences between direct and indirect estimates in all closed

Table 1

Characteristics of the included studies.

Author	Year	Register ID	Type of AMD	Types of control	Sample size	Age, y[a]	Ratio of gender (F/M)	Experimental intervention	Control	Follow-up[b]
Brain L. Yaspan[15]	2017	NCT01229215	GA secondary to AMD	Patients	129	78.7±7.3	70/53	Lampalizumab	Placebo	18 M
Chieko Shiragami[16]	2017	NA	Non-exudative AMD	Patients	52	50-85	18/30	Isopropyl unoprostone	Placebo	54 W
Yuan Tao[17]	2016	NA	DAMD	Patients	100	71±7.74	54/46	a-Lipoic acid	Placebo	3 M
Eva Rencova[18]	2015	NA	DAMD	Patients	24	64–83	NA	Rheohemapheresis	Blank	2.5 Y
Glenn J. Jaffe[19]	2015	NCT00890097	GA secondary to AMD	Patients	768	78.3±7.6	439/333	AL-8309B (tandospirone)	Placebo	36 M
Pravin U. Dugel[20]	2015	NCT01002950	GA secondary to AMD	Patients	72	80 (55-95)	47/25	Emixustat	Placebo	90 D
Zohar Yehoshua[21]	2014	NCT00935883	GA secondary to AMD	Patients	30	79±7	NA	Eculizumab	Placebo	52 W
Philip A. Petrou[22]	2015	NCT01445548	GA secondary to AMD	Eyes	6	60–84	2/4	Sirolimus	Blank	12 M
Wai T. Wong[23]	2013	NCT00766649	GA secondary to AMD	Eyes	8	68–89	3/5	Sirolimus	Blank	24 M
Nathan L. Mata[24]	2013	NCT00429936	GA secondary to AMD	Patients	246	53–90	149/97	Fenretinide	Placebo	2 Y
Jens Dawczynski[25]	2013	NCT00763659	Non-exudative AMD	Patients	172	70±10	94/78	Antioxidant complex	Placebo	12 M
M. Blaha [26]	2013	NA	Non-exudative AMD	Patients	72	54–85	54/18	Rheohemapheresis	Blank	2.5 Y
Albert J Augustin[27]	2013	NA	DAMD	Patients	36	58–95	18/18	Alprostadil	Blank	6 M
Emma Borrelli[28]	2012	NA	DAMD	Patients	140	59–81	28/112	O3-AHT (Ozonated major autohemotherapy)	Placebo	12 M
Kang Zhang[29]	2011	NCT00277134	GA secondary to AMD	Patients	51	56–88	27/24	Ciliary neurotrophic factor	Blank	12 M
Eva Rencova[30]	2011	NA	DAMD	Patients	32	57–83	26/6	Rheohemapheresis	Blank	18 M
Michael Janusz Koss[31]	2009	NA	DAMD	Patients	43	55–85	31/12	Rheohemapheresis	Blank	7.5 M
David A. Newsome[32]	2008	NA	DAMD	Patients	74	72.1±11.7	59/15	Zinc-Monocysteine	Placebo	6 M
Jose S. Pulido[33]	2006	NA	DAMD	Patients	216	50–86	100/98	Rheohemapheresis	Placebo	12 M
Stuart Richer[34]	2004	NA	DAMD	Patients	90	74.7±7.2	4/86	Lutein;Antioxidant complex	Placebo	12 M
Nuttawut Rodanant[35]	2002	NA	DAMD	Eyes	50	50–95.5	32/18	Diode laser	Blank	18 M
Richer S[36]	1996	NA	DAMD	Patients	71	72	5/66	Antioxidant complex	Placebo	18 M

AMD = age-related macular degeneration, DAMD = dry age-related macular degeneration, GA = geographic atrophy, NA = Not available.

[a] Mean ± Standard deviation; Median (minimum-maximum).

[b] D = days; W = weeks; M = months; Y = years.

loops in the network.[12] For all treatments, we estimated the ranking probability of the treatment being at each possible rank for each intervention using a surface under the cumulative ranking curve (SUCRA).[13] Comparison-adjusted funnel plots were used to determine whether small-study effects were present in our analysis.[14] We also performed subgroup analysis for all outcomes according to DAMD and GA secondary to DAMD. Standard mean differences (SMDs) with 95% confidence intervals (CIs) were calculated to determine the sizes of the effects if traditional meta-analysis was needed. All tests

Figure 1. Risk of bias graph of each of the included studies.

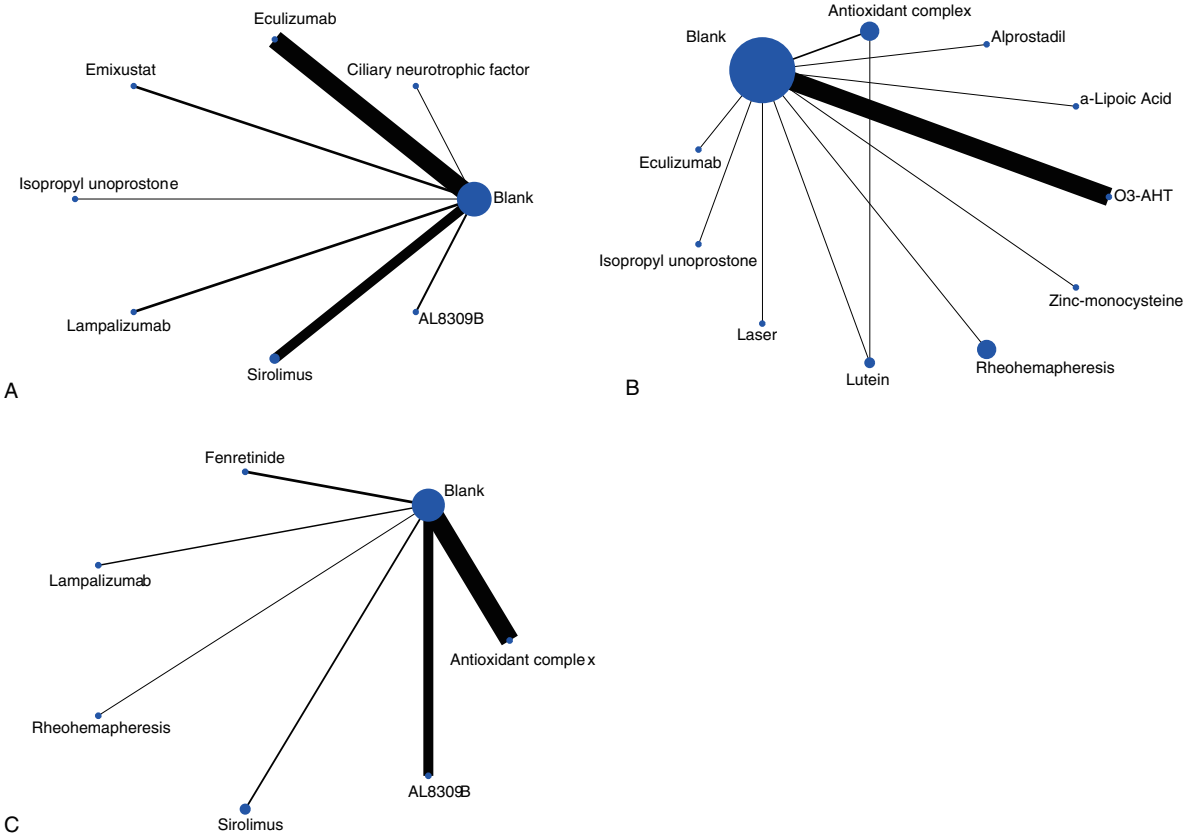

Figure 2. Network of comparisons for outcomes in the analysis. A, Change in GA area; (B) BCVA (logMAR); and (C) BCVA (letters).

were 2-tailed, and a $P < .05$ was considered statistically significant. Data analyses were performed using STATA software (version 13.0; Stata Corporation, College Station, TX).

3. Results

3.1. Literature search

In our study, 397 articles were identified after duplications were removed. A total of 348 of these articles were excluded after the titles and abstracts were screened. The full texts of the remaining 49 articles were assessed, and the following studies were excluded: irrelevant outcomes for this review defined as BCVA and GA area change (7 studies); duplicated publication (6 studies); non-DAMD patients (6 studies); non-RCTs (2 studies); and non-therapeutic study (1 study). Finally, 22 articles that assessed 2482 patients were collected in our systematic review[15–36] (Table 1).

Among the included studies, the publication year was between 1996 and 2017. The patients' age was greater than 50 years old, and the maximum age was 95.5 years. The numbers of females and males were similar. Three included studies were self-control studies that compared the study eyes and control eyes. Sixteen therapeutic regimens were included in our analysis, including O3-AHT (major ozonated autohemotherapy), a-lipoic acid, alprostadil, the antioxidant complex, ciliary neurotrophic factor, eculizumab, emixustat, fenretinide, isopropyl unoprostone (IU), lampalizumab, laser, lutein, rheohemapheresis, sirolimus, AL8309B (tandospirone), and zinc-monocysteine. The follow-up period ranged from 3 months to 2.5 years. All of the included studies were RCTs; 14 studies used assessor blinding, and 8 studies used participant and investigator blinding. The risk of bias of selective reporting and incomplete outcomes was mostly low. In addition, 7 studies were supported by drug-related manufacturers. In total, the quality of included studies was ideal (Fig. 1).

Table 2

League table for change of geographic atrophy area estimates of therapeutic strategies according to their relative effects.

Blank (33.1%)[a]							
0.34 (–0.87,1.55)	Ciliary neurotrophic factor (58.2%)						
0.00 (–0.32,0.32)	–0.34 (–1.59,0.91)	Eculizumab (34.0%)					
0.25 (–0.35,0.84)	–0.09 (–1.44,1.26)	0.25 (–0.42,0.92)	Emixustat (54.6%)				
1.08 (–0.19,2.35)	0.74 (–1.02,2.50)	1.08 (–0.23,2.39)	0.83 (–0.57,2.24)	Isopropyl Unoprostone (88.6%)			
0.20 (–0.39,0.79)	–0.14 (–1.49,1.21)	0.20 (–0.47,0.87)	–0.05 (–0.88,0.79)	–0.88 (–2.28,0.52)	Lampalizumab (51.7%)		
-0.54 (–0.89, –0.19)	–0.88 (–2.14,0.38)	**–0.54 (–1.01, –0.07)**	**–0.79 (–1.48, –0.10)**	**–1.62 (–2.94,-0.30)**	**–0.74 (–1.42, –0.06)**	Sirolimus (0.0%)	
0.62 (–0.04,1.28)	0.28 (–1.10,1.66)	0.62 (–0.11,1.35)	0.37 (–0.51,1.26)	–0.46 (–1.89,0.97)	0.42 (–0.46,1.30)	**1.16 (0.42,1.90)**	AL8309B (17.1%)

[a] The SUCRA probabilities are given in brackets; boldface font indicates that the comparison is statistically significant.

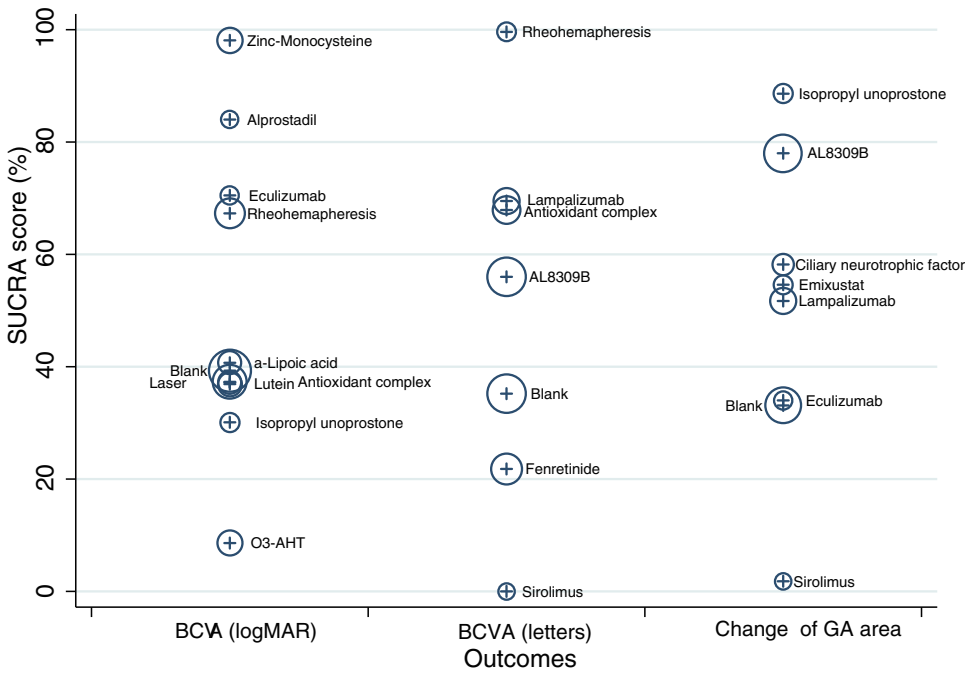

Figure 3. The SUCRA score of each intervention in all related outcomes. The circles are weighted by the square root of the sample size.

3.2. Results of network meta-analysis

For the outcome of GA area change, 8 articles had related results in network meta-analysis. The network plot showed that all treatment regimens had direct comparisons to the blank control (Fig. 2A). In the figure, the nodes were weighted according to the number of studies that evaluated each treatment, and the edges were weighted according to the precision of the direct estimate (Fig. 2A). Eculizumab versus the blank control showed the most

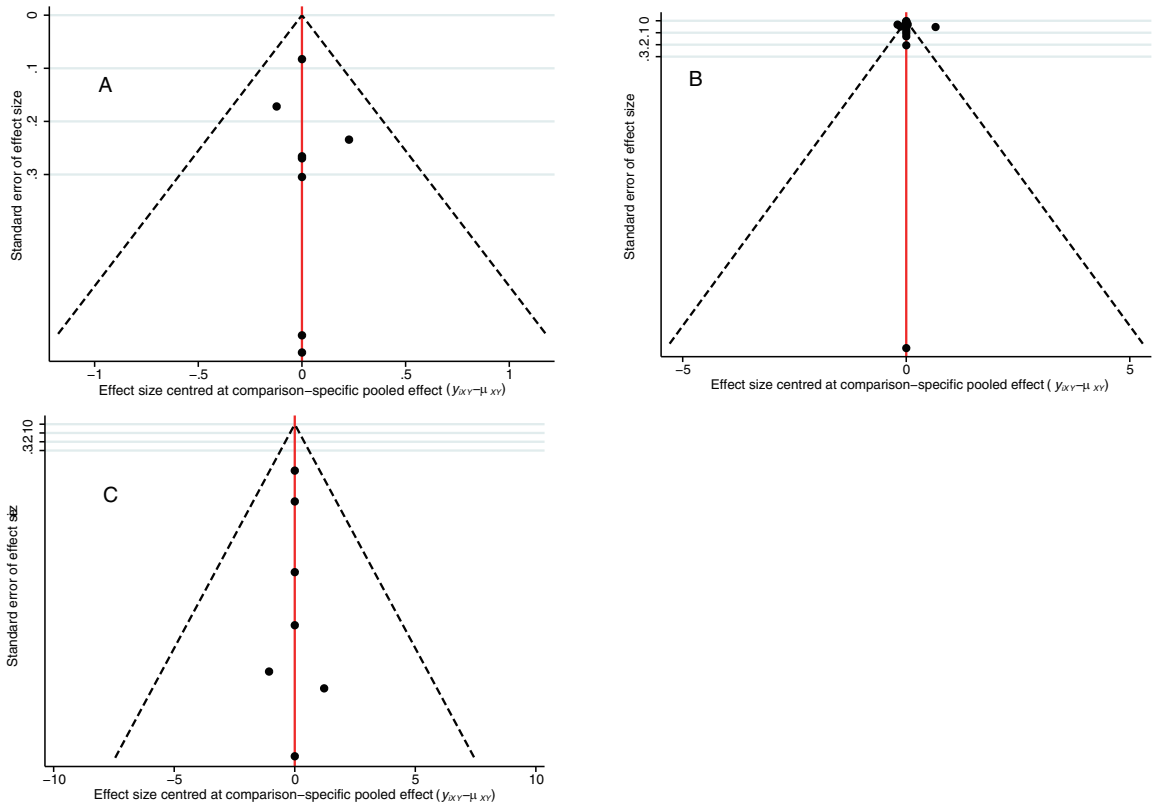

Figure 4. Comparison-adjusted funnel plot for assessing treatment effects. A, Change in GA area; (B) BCVA (logMAR); and (C) BCVA (letters).

Table 3

League table of the network meta-analysis for the BCVA (logMAR) estimates of therapeutic strategies according to their relative effects.

03-AHT (8.6%)*										
−0.49 (−1.31,0.32)	a-Lipoic Acid (40.7%)									
−1.97 (−2.87, −1.08)	**−1.48 (−2.40, −0.56)**	Alprostadil (84.0%)								
−0.44 (−1.08,0.20)	0.05 (−0.63,0.73)	**1.53 (0.76,2.31)**	Antioxidant complex (37.3%)							
−0.46 (−1.02,0.09)	0.03 (−0.57,0.63)	**1.51 (0.81,2.21)**	−0.02 (−0.35,0.31)	Blank (39.3%)						
−2.66 (−8.09,2.76)	−2.17 (−7.60,3.26)	−0.69 (−6.13,4.75)	−2.22 (−7.63,3.18)	−2.20 (−7.59,3.20)	Eculizumab (70.5%)					
−0.34 (−1.17,0.48)	0.15 (−0.70,1.00)	**1.63 (0.70,2.56)**	0.10 (−0.60,0.79)	0.12 (−0.49,0.73)	2.32 (−3.11,7.75)	Isopropyl unoprostone (30.1%)				
−0.44 (−1.24,0.36)	0.05 (−0.78,0.88)	**1.53 (0.62,2.44)**	−0.00 (−0.67,0.66)	0.02 (−0.56,0.60)	2.22 (−3.21,7.65)	−0.10 (−0.94,0.74)	Laser (37.2%)			
−0.43 (−1.19,0.33)	0.06 (−0.73,0.86)	**1.54 (0.67,2.42)**	0.01 (−0.51,0.53)	0.03 (−0.49,0.56)	2.23 (−3.19,7.65)	−0.09 (−0.89,0.72)	0.01 (−0.77,0.79)	Lutein (36.9%)		
−0.83 (−1.46, −0.21)	−0.34 (−1.00,0.32)	**1.14 (0.38,1.90)**	−0.39 (−0.83,0.05)	**−0.37 (−0.66, −0.08)**	1.83 (−3.57,7.23)	−0.49 (−1.16,0.19)	−0.39 (−1.04,0.26)	−0.40 (−1.00,0.20)	Rheohemapheresis (67.3%)	
−5.07 (−5.91, −4.23)	**−4.58 (−5.45, −3.71)**	**−3.10 (−4.04, −2.16)**	**−4.63 (−5.34, −3.92)**	**−4.61 (−5.24, −3.98)**	−2.41 (−7.84,3.02)	**−4.73 (−5.61, −3.85)**	**− 4.63 (−5.48,−3.78)**	**−4.64 (−5.46, −3.82)**	**−4.24 (−4.93, −3.55)**	Zinc-monocysteine (98.1%)

*The SUCRA probabilities are given in brackets; boldface font indicates that the comparison is statistically significant.

precision among the comparisons. There were also no loops in the network for inconsistency. In the league table, only sirolimus was inferior to other treatments (Table 2). The SUCRA result showed that IU (88.6%) might have the best GA area reduction (Fig. 3); however, there was no significant difference between IU and the blank control. The results exhibited no marked publication bias (Fig. 4A).

In the network meta-analysis, 14 articles reported BCVA (logMAR) outcomes after treatment. The eligible comparisons of BCVA (logMAR) are present in Figure 2B, which shows predominantly pair wise comparisons of different treatments for DAMD. All of the treatment regimens were directly compared with the blank control, and lutein was directly compared with the antioxidant complex. An inconsistency plot was produced to assume the loop-specific heterogeneity estimate, and the exp (IF) of lutein, the antioxidant complex, and the blank loop was non-significant (IF = 0.027; 95% CI: 0.00–0.08). In addition, global inconsistency analysis revealed no significant inconsistencies among the studies ($P = .947$). The results of the network meta-analysis are presented as a league table for all possible pair wise comparisons estimated in the network meta-analysis. Furthermore, we ranked the comparative effects of all regimens; zinc-monocysteine (98.1%) was the most likely to improve BCVA (logMAR), followed by alprostadil (84.0%), eculizumab (70.5%), and rheohemapheresis (67.3%). Other SUCRAs of regimens are shown in Table 3 and Figure 3. Additionally, the comparison-adjusted funnel plot used to assess publication bias and determine the presence of small-study effects did not suggest any publication bias (Fig. 4B).

Seven studies reported BCVA (letters) outcomes, and the eligible comparisons are shown in Figure 2C. All of the treatment regimens were directly compared with the blank control. The antioxidant complex versus the blank control showed the most precision among the comparisons. The network had no degree of freedom for inconsistency because there were no loops in the network. The league table of BCVA (letters) outcomes is shown for all possible comparisons in the network (Table 4); however, the standard errors of some results were relatively large and might affect the robustness of the results. In a ranking of the comparative effects of all treatments in BCVA (letters) with SUCRA, rheohemapheresis (99.6%), lampalizumab (69.5%), and the antioxidant complex (67.9%) showed marked benefits for BCVA (letters) recovery (Fig. 3). The comparison-adjusted funnel plot showed no potential publication bias (Fig. 4C).

In the subgroup analysis of change in GA area, we analyzed the effect of each intervention in GA patients. SUCRA ranking indicated that AL8309B (86.6%) might be the best for GA area reduction. In DAMD patients, only IU was reported and was not statistically different from the blank control (SMD: –0.491; 95% CI: –1.065 to 0.084; $P = .094$). For the BCVA (logMAR) results, there was no statistical difference between eculizumab and the blank control (SMD: 0.308, 95% CI: –0.455 to 1.072, $P = .429$) in GA patients. In the DAMD population, zinc-monocysteine (100%) might be the best. For BCVA (letters) results, lampalizumab (88.20%) was most likely to be the best in GA patients, while rheohemapheresis (99.70%) might be the best in DAMD patients (Table 5). The results of the subgroup analysis were consistent with the preliminary analysis, but reference values were still obtained for the treatment of GA and DAMD patients. For patient-reported visual outcomes, Visual Function Questionnaire (VFQ)-14 results were only reported in 1 article, with no significant differences for the lutein group, the lutein plus antioxidants group, and the placebo group.[34] In addition, 1

Table 4

League table for BCVA (letters) outcome estimates of therapeutic strategies according to their relative effects.

Antioxidant complex (67.9%)*						
1.67 (0.64,2.71)	Blank (35.2%)					
3.47 (0.00,6.93)	1.80 (-1.51,5.10)	Fenretinide (21.8%)				
–0.87 (–5.48,3.74)	–2.54 (–7.03,1.95)	–4.34 (–9.91,1.24)	Lampalizumab (69.5%)			
–10.13 (–17.61,–2.64)	**–11.80 (–19.21,–4.39)**	**–13.60 (–21.71,–5.48)**	**–9.26 (–17.93,–0.59)**	Rheohemapheresis (99.6%)		
18.44 (14.27,22.60)	**16.76 (12.73,20.79)**	**14.97 (9.75,20.18)**	**19.30 (13.27,25.34)**	**28.56 (20.12,37.00)**	Sirolimus (0.0%)	
0.62 (–1.39,2.63)	–1.05 (–2.77,0.67)	–2.85 (–6.57,0.88)	1.49 (–3.32,6.30)	**10.75 (3.14,18.36)**	**–17.81 (–22.20,–13.43)**	AL8309B (56.0%)

* The SUCRA probabilities are given in brackets; boldface font indicates that the comparison is statistically significant.

article analyzed the outcome, indicating that a-lipoic acid treatment could significantly increase the Chinese-Version Low Vision Quality of Life (CLVQOL) score in DAMD patients (SMD: 0.52; 95% CI: 0.12–0.92; $P = .10$).[17]

4. Discussion

In this study, we performed a network meta-analysis to assess the efficacy of several treatment regimens for DAMD. Zinc-monocysteine and rheohemapheresis showed significantly better effects on BCVA (logMAR) improvement, and compared with the blank control, rheohemapheresis and the antioxidant complex showed better effects on BCVA (letters) improvement. Other treatments have potential effects on DAMD, including alprostadil, eculizumab, and lampalizumab. However, there is no effective treatment for GA area reduction. The administration and dosage of each intervention included in our analysis are summarized in Table 6.[15–36]

An antioxidant repair system in the normal retina maintains the balance between oxidation and antioxidant activity. However, DAMD patients accumulate more active oxygen in the retina, which destroys the oxidation balance. Therefore, at present, antioxidant supplements are scientifically feasible for DAMD treatment. Zinc-monocysteine was analyzed separately from the antioxidant complex because it contains only zinc and cysteine components. Zinc is an essential nutrient that participates in a variety of essential biochemical reactions and removes oxygen free radicals in the body. N-acetyl-cysteine can exert antioxidant effects through a sulfhydryl donor and regenerate glutathione. Zinc-monocysteine had an ideal effect on DAMD treatment, with only 1 related study showing a non-robust result. In our results, the antioxidant complex also showed therapeutic effects on BCVA. The antioxidant complex includes lutein, multivitamin, zinc, copper, and other components.[32] Overall, this type of drug contains the main agents for preserving visual function in DAMD patients. Notably, antioxidant agents exhibited more marked improvement effects for middle- and advanced-stage patients due to increased oxidation product aggregation, while the improvement is relatively weak for early-stage patients. The varying effects of antioxidant treatment for the different stages of DAMD in patients may be worth researching in further studies. Rheohemapheresis is a special method of double plasma filtration performed to eliminate high molecular weight substances.[18] Rheohemapheresis leads to the improvement of rheological parameters and erythrocyte aggregation to improve blood flow in the choroid and increase visual function. This method had a large number of related RCTs, and the results regarding improvement in patients' visual function were robust. However, the relatively complex treatment process of rheohemapheresis may affect its clinical application.

In our study, other drugs may have potential therapeutic effects on DAMD, including alprostadil, eculizumab, and lampalizu-

Table 5

Subgroup analysis of each outcome for different types of patients.

Interventions	Change of GA area		BCVA (logMAR)		BCVA (letter)	
	GA patients, %	DAMD patients	GA patients	DAMD patients, %	GA patients, %	DAMD patients, %
O-3-AHT	-	-	-	8.60	-	-
a-Lipoic acid treatment	-	-	-	43.40	-	-
Alprostadil	-	-	-	88.80	-	-
Antioxidant	-	-	-	38.40	-	50.20
Blank control	38.00	-	-	41.10	52.50	0.10
Ciliary neurotrophic factor	64.20	-	-	-	-	-
Eculizumab	38.80	-	0.31 (-0.46,1.07)[a]	-	-	-
Emixustat	62.60	-	-	-	-	-
Fenretinide	-	-	-	-	32.20	-
Isopropyl unoprostone	-	-0.49 (-1.07,0.08)[a]	-	30.10	-	-
Lampalizumab	57.70	-	-	-	88.20	-
Laser	-	-	-	39.30	-	-
Lutein	-	-	-	38.20	-	-
Rheohemapheresis	-	-	-	72.10	-	99.70
Sirolimus	2.10	-	-	-	0	-
AL8309B	86.60	-	-	-	77.10	-
Zinc-monocysteine	-	-	-	100	-	-

AMD = age-related macular degeneration, DAMD = dry age-related macular degeneration, GA = geographic atrophy.

[a] Standard means difference (SMD) with 95% confidence intervals (CIs) results compared with the blank control by traditional meta-analysis.

Table 6

Administration and dosage of each of the interventions included in our analysis.

Interventions	Administration	Dose
Major ozonated autohemotherapy (O-3-AHT) [28]	Intravenous (blood mixed with O_3)	225 mL blood twice weekly
a-Lipoic acid treatment [17]	Oral	0.2 g/day
Alprostadil [27]	Intravenous	60 μg/day for 3 weeks
Antioxidant complex [25]	Oral	1 mg zeaxanthin+O-3-LCPUFAS (100 mg DHA+30 mg EPA)+antioxidants once or twice daily
Antioxidant complex [34]	Oral	Antioxidant and nutrients (OcuPower, Boynton beach, FL)
Antioxidant complex [36]	Oral	"Broad-spectrum" antioxidant capsule twice daily
Ciliary neurotrophic factor [29]	Intraocular implant	5 ng/20 ng per day
Eculizumab [21]	Intravenous	600 mg weekly/900 mg every 2 weeks
ACU-4429 (Emixustat) [20]	Oral	2 mg/5 mg/7 mg/10 mg every morning
Fenretinide [24]	Oral	100 mg/300 mg daily
Isopropyl unoprostone ophthalmic solution [16]	Topical	0.15%
Lampalizumab [15]	Intravitreal	10 mg/100 μL monthly/every other month
Infrared (810-nm) diode laser [35]	Local application	Forty-eight diode laser lesions were applied in four concentric circles outside the foveal avascular zone.
Lutein [25,34]	Oral	10 mg once or twice daily
Rheohemapheresis [18,26,30,31,33]	Intravenous	100%–150% of patient's plasma volume per treatment (40 mL × body weight) × 8 times
Sirolimus [22,23]	Intravitreal/Subconjunctival injection	2% (440 μg/20 μL) injection
AL-8309B (Tandospirone) [19]	Topical	1.0%/1.75% twice daily
Zinc-monocysteine [32]	Oral	25 mg twice daily for 6 months

mab. Intravenous alprostadil is a drug form of prostaglandin E1 that can improve microcirculation in DAMD eyes via regulation of platelet function, antioxidation, and inhibition of pro-inflammatory factor release.[27] Eculizumab is a humanized monoclonal antibody derived from the murine anti-human C5 antibody[21]; it inhibits C5, prevents terminal complement activation, and blocks formation of the membrane attack complex. Although our study determined that eculizumab is ineffective at reducing GA area, eculizumab might play a role in relieving patients' visual function. Lampalizumab is an antigen-binding fragment of a humanized monoclonal antibody directed against complement factor D, a potential therapeutic target for GA treatment.[15] Although these treatments were not significantly different from the blank control, there was still an advantage over other treatments in the network meta-analysis.

The current interventions were able to improve only the DAMD patients' visual function and had no effect on GA reduction. Since the pathological process of GA is not fully understood, there is no specific treatment for the condition. Stem cells, as a current therapeutic trend, have also been used in DAMD treatment, but there are no published RCTs. Cytotherapy is mainly used to induce cells transplanted to the atrophic area to relieve disease progression. The treatment effect is based on the differentiation of transplanted cells into retinal pigment epithelial cells or other related cells and regulation of the microenvironment by cytokines. In addition, intravitreal injection of autologous bone-marrow stem cells (ABMSCs) in DAMD treatment has been applied in a clinical non-randomized trial and showed a slight improvement effect for visual acuity; however, large scale RCTs are needed to confirm these results (NCT01518127).[37]

In conclusion, zinc-monocysteine and rheohemapheresis show significantly better effects on BCVA (logMAR) improvement; compared with the blank control, rheohemapheresis and the antioxidant complex show better effects on BCVA (letters) improvement. Other treatments have potential effects on DAMD, including alprostadil, eculizumab, and lampalizumab.

4.1. Limitations

There are several notable limitations in this study. First, our study was conducted on the study level instead of the individual level; second, DAMD patients were not classified according to the stage of the disease; third, the drug dose was neglected in the network analysis; and fourth, the length of follow-up was not further analyzed, although some studies showed that drugs might have better effects in the short-term but not in the long-term.

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