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

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

Yanli Wei, MM, Hongxia Liao, MM, Jian Ye, MD

#### 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
- CI = confidence intervals
- OLIVOL = 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 = retina 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%. At present, AMD is a major cause of vision loss worldwide. In 2015, there were 8.4 million patients with moderate to severe vision impairment caused by AMD. 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. 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.

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 visual function.
visual acuity (BCVA) and GA area change. New therapies for these related pathways are under investigation. In addition, new non-invasive inspection methods have provided evaluation tools for clinical research. 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 Reviews and Meta-Analysis for Network Meta-Analysis (PRISMA-NMA) guidelines. 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

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,” “non-exudative,” “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.

2.2. Data extraction and quality assessment

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. 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 loops.

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.

2.3. Statistical analysis

Table 1

| Author                  | Year   | Register ID | Type of AMD                   | Types of control | Sample size | Age, y± | Ratio of gender (F/M) | Experimental intervention | Control | Follow-up |
|-------------------------|--------|-------------|-------------------------------|------------------|-------------|---------|-----------------------|---------------------------|---------|-----------|
| Brau L. Yapici[14]      | 2017   | NCT01229215 | GA secondary to AMD           | Patients         | 129         | 78.7±3.7 | 70/53                | Lampalizumab              | Placebo | 18 M      |
| Chielski Shragan[36]    | 2017   | NA          | Non-exudative AMD             | Patients         | 52          | 50-85    | 18/30                | Isopropyl unoprostone     | Placebo | 54 W      |
| Yuan Tai[17]            | 2016   | NA          | DAMD                          | Patients         | 100         | 71±7.4  | 54/46                | alpha-Lipoic acid         | Placebo | 3 M       |
| Eva Rienceau[14]        | 2016   | NA          | DAMD                          | Patients         | 24          | 64-83    | NA                   | Rheohemapheresis          | Blank   | 2.5 Y     |
| Glenn J. Jaffe[14]      | 2015   | NCT00890097 | GA secondary to AMD           | Patients         | 768         | 78.3±7.6 | 439/333              | AL-9300B (tandospirone)   | Placebo | 36 M      |
| Pranii U. Ogle[34]      | 2015   | NCT01002950 | GA secondary to AMD           | Patients         | 72          | 80 (55-95)| 47/25                | Emsilastat                | Placebo | 90 D      |
| Zohar Yehoshua[22]      | 2014   | NCTPHJ058883 | GA secondary to AMD           | Patients         | 30          | 79±7    | NA                   | Ezuluzamb                  | Placebo | 52 W      |
| Philip A. Petrou[22]    | 2015   | NCT01445548 | GA secondary to AMD           | Eyes             | 6           | 60-84   | 2/4                  | Siroiinu                   | Blank   | 12 M      |
| Wai T. Wong[22]         | 2013   | NCTPHJ06649 | GA secondary to AMD           | Eyes             | 8           | 68-89   | 3/5                  | Siroiinu                   | Blank   | 24 M      |
| Nathan L. Malik[22]     | 2013   | NCT00429936 | GA secondary to AMD           | Patients         | 246         | 53-80   | 148/87              | Beferolide                 | Placebo | 2 Y       |
| Jens Dawczyk[22]        | 2013   | NCTPHJ073569 | Non-exudative AMD              | Patients         | 172         | 70±10   | 94/78               | Antioxidant complex        | Placebo | 12 M      |
| M. Blisha[35]           | 2013   | NA          | Non-exudative AMD             | Patients         | 72          | 54-85   | 54/18               | Rheohemapheresis           | Blank   | 2.5 Y     |
| Albert J. Augustyn[27]  | 2012   | NA          | DAMD                          | Patients         | 36          | 56-95   | 19/18               | Aprostadil                 | Blank   | 6 M       |
| Emma Berrell[38]        | 2012   | NA          | DAMD                          | Patients         | 140         | 59-81   | 28/112              | O3-KHT (Conradt major autohemotherapy) | Placebo | 12 M      |
| Kang Zhang[39]          | 2011   | NCTPHJ0277134 | GA secondary to AMD           | Patients         | 51          | 56-88   | 27/04               | Stabilization of photoreceptors | Blank   | 12 M      |
| Eva Rienceau[14]        | 2011   | N/A         | DAMD                          | Patients         | 32          | 57-83   | 26/8                | Rheopexysynthesis           | Blank   | 18 M      |
| Michael Janecz Kast[11] | 2009   | NA          | DAMD                          | Patients         | 43          | 55-85   | 31/12               | Rheohemapheresis           | Blank   | 7.5 M     |
| David A. Neumann[27]    | 2008   | NA          | DAMD                          | Patients         | 74          | 72±11.7 | 59/15               | Zinc Monocystine           | Placebo | 6 M       |
| Jose S. Patj[27]        | 2006   | NA          | DAMD                          | Patients         | 216         | 50-86   | 100/18              | Rheohemapheresis           | Placebo | 12 M      |
| Stueart Richer[44]      | 2004   | NA          | DAMD                          | Patients         | 90          | 74.7±2.7 | 4/86                | Lucon/Antioxidant complex  | Placebo | 12 M      |
| Nuttawut Rodan minded[20] | 2002 | NA         | DAMD                          | Eyes             | 50          | 50-95.5 | 32/18               | Diode laser                | Blank   | 18 M      |
| Richer S[27]            | 1996   | NA          | DAMD                          | Patients         | 71          | 72      | 5/6                 | Antioxidant complex        | Placebo | 18 M      |

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

* Mean±Standard deviation; Median (minimum−maximum).

D = days; W = weeks; M = months; Y = years.
loops in the network. 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). Comparison-adjusted funnel plots were used to determine whether small-study effects were present in our analysis. 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
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).

![Network of comparisons for outcomes in the analysis. A, Change in GA area; (B) BCVA (logMAR); and (C) BCVA (letters).](image-url)

Table 2

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

| Strategy                  | SUCRA Probability (%) | Change in GA Area (95% CI) |
|---------------------------|-----------------------|-----------------------------|
| Blank                     | 33.1%                 | -0.34 (-0.87, 1.55)         |
| Ciliary neurotrophic factor | 58.2%                 | -0.25 (-0.35, 0.84)         |
| Eculizumab                | 54.0%                 | -0.74 (-1.02, 0.50)         |
| Emixustat                 | 54.6%                 | -0.10 (-0.23, 0.09)         |
| Isopropyl unoprostone     | 84.0%                 | 0.20 (-0.39, 0.79)          |
| Lampalizumab              | 51.7%                 | -0.54 (-1.49, 0.38)         |
| Sirolimus                 | 0.0%                  | -0.88 (-2.00, 0.28)         |
| AL8309B                   | 17.1%                 | -0.54 (-2.14, 0.00)         |

* The SUCRA probabilities are given in parentheses; boldface indicates that the comparison is statistically significant.
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 3. The SUCRA score of each intervention in all related outcomes. The circles are weighted by the square root of the sample size.

Figure 4. Comparison-adjusted funnel plot for assessing treatment effects. A, Change in GA area; (B) BCVA (logMAR); and (C) BCVA (letters).
League Table of the network meta-analysis for the BCVA (logMAR) estimates of therapeutic strategies according to their relative effects.

| Therapeutic Strategy          | SMD (95% CI)        | RRR (95% CI)       |
|------------------------------|---------------------|--------------------|
| O3-AHT (8.6%)                | 0.49 (-1.31, 0.32)  | 1.08 (-1.02, 0.09) |
| a-Lipoic Acid (40.7%)        | -0.02 (-0.35, 0.31) | 1.48 (0.56, 0.63) |
| Alprostadil (84.0%)          | 0.05 (-0.63, 0.73)  | 1.53 (0.76, 2.31)  |
| Eculizumab (70.5%)           | -0.10 (0.60, 0.79)  | 0.12 (-0.49, 0.56) |
| Laser (37.2%)                | 0.01 (-0.51, 0.53)  | 0.03 (-0.49, 0.56) |
| Zinc-monocysteine (98.1%)    | 0.10 (-0.89, 0.72)  | 0.01 (-0.83, 0.83) |
| Blank (39.3%)                | -0.39 (-1.04, 0.26) | -0.66 (-3.98, 3.92) |

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

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. In addition, 1
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 effective treatment for GA area reduction. The administration and dosage of each intervention included in our analysis are robust. However, the relatively complex treatment process of rheohemapheresis may affect its clinical 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 lampalizumab.

### Table 4
League table for BCVA (letters) outcome estimates of therapeutic strategies according to their relative effects.

| Antioxidant complex (87.9%) | Blank (35.2%) | Ferentide (21.8%) | Lampalizumab (69.5%) | Rheohemapheresis (99.6%) | Sirolimus (0.0%) | AL8309B (56.0%) |
|---------------------------|--------------|------------------|----------------------|--------------------------|-----------------|-----------------|
| 1.67 (0.64,2.71)          | 1.80 (-1.51,5.10) | -0.34 (-9.91,1.24) | -10.26 (-17.93,-0.59) | -0.75 (-3.47,2.07) | -1.67 (0.64,2.71) | -1.39 (-2.64,0.95) |

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

### Table 5
Subgroup analysis of each outcome for different types of patients.

| Interventions                  | GA patients, % | DAMD patients, % | BCVA (logMAR) | BCVA (letter) |
|--------------------------------|----------------|------------------|---------------|---------------|
| 0-3-AHT                        | -              | -                | 8.60          | -             |
| a-Lipoic acid treatment        | -              | -                | -             | -             |
| Alprostadil                    | -              | -                | 43.40         | -             |
| Antioxidant                    | -              | -                | 88.80         | -             |
| Blank control                  | 38.00          | -                | 41.10         | 52.50         |
| Ciliary neurotrophic factor    | 64.20          | -                | 0.31 (-0.46,1.07) | -           |
| Eculizumab                     | 38.80          | -                | -             | -             |
| Emixustat                      | 62.60          | -                | -             | -             |
| Fenretide                      | -              | -                | 38.40         | 50.20         |
| Isopropyl unoprostone          | -              | -                | 41.10         | 52.50         |
| Lampalizumab                   | 57.70          | -                | 0.31 (-0.46,1.07) | -           |
| Laser                          | -              | -                | 38.40         | 50.20         |
| Sirolimus                      | 2.10           | -                | 38.40         | 50.20         |
| AL8309B                        | 86.60          | -                | 2.10           | 99.70         |
| Zinc-monocysteine              | -              | -                | 100           | -             |

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

*Standard means difference (SMD) with 95% confidence intervals (CIs) results compared with the blank control by traditional meta-analysis.
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. Cytoreduction 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).[17]

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.

### Author contributions

Conceptualization: Jian Ye.
Data curation: Yanli Wei.
Formal analysis: Jian Ye.
Investigation: Yanli Wei, Hongxia Liao.
Resources: Hongxia Liao.
Software: Hongxia Liao.
Supervision: Hongxia Liao.
Validation: Hongxia Liao.
Visualization: Hongxia Liao.
Writing – original draft: Yanli Wei, Jian Ye.
Writing – review & editing: Jian Ye.

### References

[1] Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health 2014;2:e106–16.
[2] Lim LS, Mitchell P, Seddon JM, et al. Age-related macular degeneration. Lancet 2012;379:1728–38.
[3] Flaxman SR, Bourne RRA, Resnikoff S, et al. Global causes of blindness and distance vision impairment 1990–2020: a systematic review and meta-analysis. Lancet 2012;379:1211–34.
[4] Sacconi R, Corbelli E, Querques G, et al. A review of current and future management of geographic atrophy. Ophthal Mon 2017;66:9–77.
[5] Chakravarthy U, Wong TY, Fletcher A, et al. Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. BMC Ophthalmol 2010;10:31.
[6] Holz FG, Straus EC, Schmitz-Valckenberg S, et al. Geographic atrophy: clinical features and potential therapeutic approaches. Ophthalmology 2014;121:1079–91.

[7] Li H, Chintalapudi SR, Jablonski MM. Current drug and molecular therapies for the treatment of atrophic age-related macular degeneration: phase I to phase III clinical development. Expert Opin Investig Drugs 2012;26:1103–14.

[8] Sadda SR, Chakravarthy U, Birch DG, et al. Clinical endpoints for the study of geographic atrophy secondary to age-related macular degeneration. Retina 2016;36:1806–22.

[9] Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of healthcare interventions: checklist and explanations. Ann Intern Med 2015;162:777–84.

[10] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

[11] Ades AE, Lu G, Higgins JP. The interpretation of random-effects meta-analysis in decision models. Med Decis Making 2005;25:646–54.

[12] Bucher HC, Guyatt GH, Griffith LE, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997;50:683–91.

[13] Li D, Wang T, Shen S, et al. Effects of fluoroquinolones in newly diagnosed, sputum-positive tuberculosis therapy: a systematic review and network meta-analysis. PLoS One 2015;10:e0145066.

[14] Trinquart L, Chatellier G, Ravaud P. Adjustment for reporting bias in network meta-analysis of antidepressant trials. BMC Med Res Methodol 2012;12:150.

[15] Yaspan BL, Williams DF, Holz FG, et al. Targeting factor D of the alternative complement pathway reduces geographic atrophy progression secondary to age-related macular degeneration. Sci Transl Med 2017;9:eaaf1443.

[16] Shiragami C, Miyake M, Fujisawa A, et al. Effect of topical isopropyl unoprostone on macular atrophy progression in eyes with exudative age-related macular degeneration. Medicine (Baltimore) 2017;96:e6422.

[17] Tao Y, Jiang P, Wei Y, et al. alpha-lipoic acid treatment improves Vision-Related Quality of Life in patients with dry age-related macular degeneration. Tohoku J Exp Med 2016;240:209–14.

[18] Rencova E, Blaha M, Studnicka J, et al. Preservation of the photoreceptor layer in geographic atrophy secondary to age-related macular degeneration: the GATE study. Am J Ophthalmol 2015;160:1226–34.

[19] Dugel PU, Novack RL, Caskey KG, et al. Phase ii, randomized, placebo-controlled, 90-day study of eumexastr hydrochloride in geographic atrophy associated with dry age-related macular degeneration. Retina 2015;35:1173–83.

[20] Yehoshua Z, de Amorim Garcia Filho CA, Nunes RP, et al. Systemic complement inhibition with eculizumab for geographic atrophy in age-related macular degeneration: the COMPLETE study. Ophthalmology 2014;121:693–701.

[21] Petros PA, Cunningham D, Shmel K, et al. Intravitreal sirolimus for the treatment of geographic atrophy: results of a phase III clinical trial. Invest Ophthalmol Vis Sci 2014;56:330–8.