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Short-term Efficacy and Safety of Biological Tear Substitutes and Topical Secretagogues for Dry Eye Disease: A Systematic Review and Network Meta-analysis

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Purpose: The purpose of this study was to assess short-term efficacy and safety of tear promotion eye drops (biological tear substitutes and topical secretagogues) for treating dry eye disease.

Methods: Randomized controlled trials comparing short-term effects of biological tear substitutes or topical secretagogues versus placebo or other topical dry eye treatments in adults with dry eye disease were identified from the MEDLINE, Embase, Scopus, ClinicalTrials.gov, and World Health Organization International Clinical Trials Registry Platform databases. Pairwise meta-analysis and network meta-analysis were performed. Outcomes were ocular symptoms, ocular surface staining, tear break-up time, Schirmer test, and adverse events. The certainty of evidence was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluations approach.

Results: Thirty-nine randomized controlled trials (3693 patients) were eligible. Using artificial tears as a reference, autologous platelet lysate was the most effective treatment for lowering ocular surface disease index (unstandardized mean difference [USMD] −31.85; 95% confidence interval [CI]: −43.19 to −20.51) and platelet rich plasma showed the most reduction in corneal fluorescein staining scores (standardized mean difference −2.52; 95% CI: −3.23 to −1.82). Cord blood serum was the most effective treatment for increasing tear break-up time (USMD 2.67; 95% CI: 0.53–4.82), and eledoisin was superior to others in improving Schirmer scores (USMD 2.28; 95% CI: 0.14–4.42). Most interventions did not significantly increase ocular adverse events compared with artificial tears.

Conclusions: Biological tear substitutes, including autologous serum, autologous platelet lysate, platelet rich plasma, and cord blood serum, might be the most effective treatment among tear promotion eye drops in relieving dry eye symptoms without increasing adverse events. However, there remains uncertainty around these findings because of low/very low certainty of evidence.

Key Words: biological tear substitutes, secretagogues, dry eye disease, network meta-analysis

(*Cornea* 2022;41:1137–1149)

Dry eye is a multifactorial disease of the ocular surface, with higher prevalence among women and elderly individuals.[1,2] Loss of tear film homeostasis in dry eye disease (DED) results in symptoms of eye irritation, redness, and visual disturbance. Although not life-threatening, DED negatively affects common activities of daily living, such as reading, driving, computer use, performing professional work, and watching television, and substantially reduces quality of life.[3–5] The overall burden of DED on the American health care was estimated at 3.84 billion US dollars per year (55.4 billion US dollars from a societal perspective).[6]

A stepwise treatment approach to DED has been recommended based on severity and etiology of the disease.[7] Initial management of DED includes health education, environmental modification, and artificial tears. If the strategies in the first step are inadequate, further advanced treatment options, including tear conservation with punctal occlusion or moisture chamber spectacles/goggles, in-office treatments, and prescription drugs specifically designed for DED, should be considered.[7] According to the pathophysiology of DED, besides artificial tears, topical medications that

Received for publication May 24, 2021; revision received October 6, 2021; accepted October 7, 2021. Published online ahead of print December 20, 2021.

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The authors have no funding or conflicts of interest to disclose.

P. Jongkhajornpong was the principal researcher with responsibility for protocol writing and PROSPERO submission. Searching for eligible studies was performed by P. Jongkhajornpong and K. Lekhanont. Both P. Jongkhajornpong and T. Anothaisintawee performed data extraction, risk of bias assessment, and GRADE analysis. All authors were involved in data analysis and writing of the manuscript. The final version of the manuscript was read and approved by all authors.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.corneajrnl.com).

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primarily aim to restore normal amount of tears are tear secretagogues and biological tear substitutes. Although several systematic reviews and meta-analyses evaluating the efficacy of either topical tear secretagogues or biological tear substitutes compared against artificial tears or placebo have been reported,[8–14] there are no studies simultaneously comparing the efficacy of topical tear secretagogues and biological tear substitutes for patients with dry eye. The recent systematic review of the efficacy and safety of topical ophthalmic drugs in the treatment of DED included 26 randomized controlled trials (RCTs) of 4 different drug groups (topical immunomodulators/antiinflammatory drugs, lymphocyte function-associated antigen 1 antagonist, tear secretagogues, and other investigational drugs targeting additional novel pathways).[15] However, studies of biological tear substitutes were not included in this review. In addition, meta-analytic approaches were not applied. Given the absence of trials involving a direct comparison of various kinds of tear promotion eye drops (artificial tears, topical secretagogues, and biological tear substitutes), the use of network meta-analysis framework could allow the integration of multiple direct and indirect comparisons of these medications, provide estimates of relative treatment effect between them, and potentially generate a hierarchy among available treatments. Therefore, we conducted a network meta-analysis (NMA) to systematically compare and rank these medications regarding their efficacy and safety in the treatment of DED.

METHODS

This systemic review and NMA was undertaken and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for systematic reviews incorporating network meta-analyses of health care interventions. The review protocol was registered in the PROSPERO database (CRD42019145555) and was approved by the Ethics Committee of Ramathibodi Hospital, Mahidol University (No. MURA2020/381).

Search Strategy and Selection Criteria

Relevant RCTs were identified from MEDLINE through PubMed, Embase, and Scopus through March 22, 2021. Unpublished and in-press studies were identified from Scopus, ClinicalTrials.gov, and World Health Organization International Clinical Trials Registry Platform. The search terms and strategy were constructed based on population (ie, dry eye) and intervention (ie, topical secretagogues and biological tear substitutes) domains without language or year restrictions (Appendix 1, Supplemental Digital Content 1, http://links.lww.com/ICO/B328). Two reviewers (P.J. and K.L.) independently selected studies based on the following inclusion criteria: 1) RCTs that were conducted in patients with dry eye aged 18 years and older; 2) studies compared the efficacy or safety of biological tear substitutes or topical secretagogues with placebo, artificial tears, or other topical dry eye treatments; and 3) studies reported at least 1 clinical outcome either symptoms or signs related to DED. We excluded phase II studies which investigated the effect of different concentrations of the same treatment and studies with insufficient data after 3 attempts of contact with study authors. Any discrepancies between both reviewers were resolved by consensus of the team.

Outcome Measures

Short-term outcomes at 2 to 12 weeks after receiving treatments were considered for the analysis. Primary outcomes were dry eye symptoms and ocular surface staining. However, there was a wide variation in choice of primary outcome measure between studies. To accommodate different primary outcome measures among the included studies, we considered the measures that were standardized and used in most studies [ie, ocular surface disease index (OSDI) and corneal fluorescein staining] as the main outcomes for the analysis. Secondary outcomes included tear break-up time (TBUT), Schirmer test (ST), and ocular adverse events. Other dry eye measures, including tear osmolarity, tear meniscus height, meibum quality and expressibility, corneal sensitivity, higher order aberration, ocular protection index, tear clearance rate, and impression cytology, were not evaluated because of the insufficient number of studies for pooling.

Data Extraction and Risk of Bias Assessment

Data were extracted independently by 2 reviewers (P.J. and T.A.). For studies reporting outcomes at multiple time points, the outcomes measured at the last visit was extracted. WebPlotDigitizer was used to extract data from figures.[16] For studies evaluating several concentrations of the same intervention, the arm that used the commercially available concentration or maximum concentration was selected. Multiple arms of the same intervention at the same concentration or different types of artificial tears were collapsed into a single arm. Different types of artificial tears among included studies were considered as a single intervention because there was no difference in clinical efficacy among different types of artificial tears.[17–23]

The quality of studies was independently assessed by 2 reviewers (P.J. and T.A.) using the Cochrane Collaboration tool for assessing risk of bias in randomized trials (RoB 2).[24] Disagreements between both reviewers were resolved by consensus.

Data Analysis

Direct meta-analysis was performed for each pair of treatment comparison if at least 2 studies were available. For continuous outcomes, unstandardized mean difference (USMD) was estimated if all studies used similar reporting tools for outcome measures; otherwise, standardized mean difference (SMD) was applied using a Cohen method. Given an assumption of well randomization, mean changes and mean at end values were combined in pooling effect size. In crossover RCTs, only data from the initial period were used. For paired-eye RCT design, variance of the mean difference was calculated by accounting for within subject correlations using a Pearson coefficient[25] and a Monte Carlo simulation

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with 1000 iterations. For adverse events, the risk ratio was estimated, regardless of correlated data.

Each relative treatment effect was pooled using the fixed-effect model if heterogeneity was absent; otherwise, a random-effect model was applied. Heterogeneity was assessed using a Cochran Q test and I^2 statistic. Heterogeneity was defined if the *P* value from the Q test is <0.1 or the I^2 statistic is $>25\%$. Sources of heterogeneity (ie, participant characteristics, dry eye etiology, and severity of DED) were explored. Subgroup analyses were performed on variables that decreased I^2 or tau^2. The severity of DED was classified as moderate to severe if the presence of any of the following: ST $\leq$ 5 mm, TBUT $\leq$ 5 seconds, recalcitrant to conventional treatments, or stated by the authors in the inclusion criteria. TBUT and ST were arbitrarily used to determine the severity of DED in our study because there was limited information on the disease severity described in the included RCTs. Most of them reported TBUT and ST being measured in the same manner, whereas dry eye symptoms and ocular surface staining were measured and scaled variously among the studies. In addition, regarding the DEWS II Diagnostic Methodology Report,[26] TBUT and ST are the 2 variables that have their clear cutoff values arranged to classify the DED severity. Publication bias was assessed by the Egger test.

The network was constructed along with a contribution plot. Artificial tears, which were the most common comparator, were assigned as a reference. Two-stage NMA was applied to estimate relative treatment effects. SMD/USMD was pooled across all studies using multivariate meta-analysis with a consistency model. The consistency assumption was assessed using global (design-by-treatment interaction model) and local (loop-specific and node-splitting methods) approaches. Inconsistency factors (IF) were estimated, and sensitivity analyses were performed accordingly. All interventions were ranked using the surface under the cumulative ranking curve (SUCRA). A comparison-adjusted funnel plot was used to assess whether results from imprecise trials differed from more precise trials.[27] Scatter plots of multiple clinical outcomes were constructed to provide an overview of all treatment outcomes. A clustered rank plot between SUCRAs of all treatment efficacy and ocular adverse events was constructed to simultaneously demonstrate the benefit and risk of all interventions. Transitivity was checked by exploring distributions of possible effect modifiers (ie, countries, sex, surgery-related DED, the portion of patients with Sjögren's syndrome, and severity of DED). All statistical analyses were performed using Stata version 16.0 (Stata Corp LP; College Station, TX).

The certainty of evidence for primary outcomes was assessed independently by 2 reviewers (P.J. and T.A.) using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach.[28–32] Disagreements between both reviewers were resolved by consensus.

RESULTS

Search Results

Thirty-nine studies (studies/patients; N/n = 39/3693) published between 1991 and 2021 were eligible from the 1766 identified studies (Fig. 1 and Table 1). All included studies were listed in Appendix 2 (Supplemental Digital Content 1, http://links.lww.com/ICO/B328). There were 10 single interventions including 4 biological tear substitutes, autologous or allogeneic serum (AS), cord blood serum (CBS), autologous platelet lysate (APL) and platelet rich plasma (PRP), and 6 topical secretagogues, diquafosol, rebamipide, eledoisin, 3-isobutyl-1-methylxanthine (IBMX), recombinant human nerve growth factor (rhNGF), and small molecule nerve growth factor peptidomimetic (MIM-D3). Two combination interventions were diquafosol plus artificial tears (DT) and rebamipide plus artificial tears (RT). Most studies were conducted in Asia (66.7%). Over half of studies were single-center (56.4%) and parallel RCTs (76.9%). The mean age was 54 years (range: 25–72.6 years), and an average female proportion was 74.4%. The median treatment duration was 4 weeks with mean baseline OSDI score, TBUT, and Schirmer score of 37, 3.6 seconds, and 5.8 mm, respectively. Nineteen (48.7%) and 4 studies (10.3%) were conducted in patients with moderate-to-severe and mild-to-moderate dry eyes, respectively, whereas 16 studies (41%) were conducted in patients with mixed/unspecified severity. Most studies (25 studies, 64%) used artificial tears as a comparator. Among them, 0.1% to 0.3% sodium hyaluronic acid was the most common lubricant used (12 studies, 48%), followed by Soft Santear (6 studies, 24%), Refresh (1 study, 4%), Systane (1 study, 4%), mixed types of artificial tears (1 study, 4%), and not specified in 4 studies (16%).

Risk of Bias Assessment

Most studies were classified as high risk of bias (range: 57.14%–68.18%), followed by some concerns (range: 26.47%–38.10%) and low risk of bias (range: 4.55%–5.88%) (Appendix 3, Supplemental Digital Content 1, http://links.lww.com/ICO/B328).

Dry Eye Symptom Scores

Thirty-four of 39 studies (2797 patients) reported symptom scores using 11 different symptoms scales, that is, the OSDI (N/n = 17/1178), 4-point scale with 2 to 12 questions (N/n = 9/988), the Dry Eye–Related Quality-of-Life Score (N/n= 2/107), the Symptom Assessment in Dry Eye (N/n = 2/295), visual analog scales (N/n = 1/20), the McMonnies score (N/n= 1/144), 101-point scale with 12 questions (N/n = 1/32), and 5-point scale (N/n = 1/33). As mentioned in the methods, only studies reporting OSDI were considered for pooling because OSDI was standardized and used in most studies. Lower OSDI scores indicated better treatment results.

Direct Meta-analysis

Four comparisons were available for pooling: diquafosol versus artificial tears (N/n = 4/374), AS versus artificial tears (N/n = 3/56), DT versus artificial tears (N/n = 2/244), and diquafosol versus cyclosporine A (CSA; N/n = 2/133) (Appendix 4, Supplemental Digital Content 1, http://links.lww.com/ICO/B328). Diquafosol, AS, and DT significantly improved OSDI scores compared with artificial tears with

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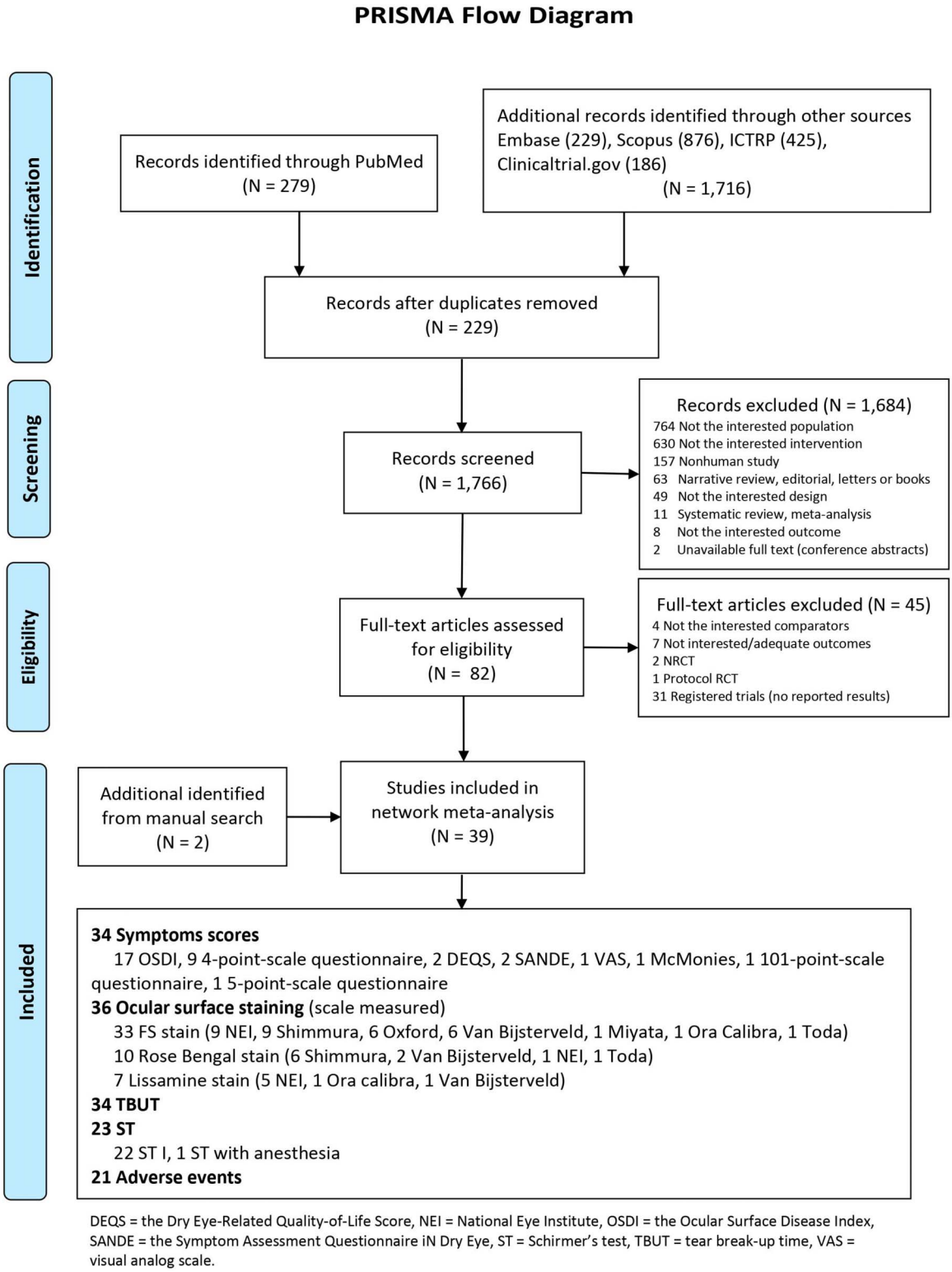

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. DEQS, Dry Eye–Related Quality-of-Life Score; FS, fluorescein; ICTRP, International Clinical Trials Registry Platform; NRCT, non-randomised controlled trial; NEI, National Eye Institute; SANDE, Symptom Assessment In Dry Eye; VAS, visual analog scale. (The full color version of this figure is available at www.corneajrnl.com.)

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TABLE 1. Characteristics of 39 Included RCTs

Author, Year	Country	Study Design	Multicenter/ Single-center	No. of Patients	Specific Condition	Intervention	Comparator	Female (%)	SS (%)	Dosage (times/d)	Follow-up (wk)	Reported Outcomes
Gilbard, 1991[e1]	United States	Paired-eye RCT	Single-center	9	NA	IBMX	Placebo	100	NA	6	4	OSS, ST,* tear osmolarity, and AE
Baek, 2016[e2]	Korea	Paired-eye RCT	Single-center	32	Postcataract surgery	3% DQ	Placebo	72.2	0	4	8	OSDI, OSS, TBUT, ST, and TMH
Kamiya, 2012[e3]	Japan	Paired-eye RCT	Multicenter	32	NA	3% DQ	AT (0.1% SH)	81.2	NA	6	4	Symptoms (101-point scale), OSS, TBUT, ST, and AE
Takamura, 2012[e4]	Japan	RCT	Multicenter	286	NA	3% DQ	AT (0.1% SH)	85.7	23.8	6	4	Symptoms (4-point scale), OSS, TBUT,* and AE*
Gong, 2015[e5]	China and Singapore	RCT	Multicenter	497	NA	3% DQ	AT (0.1% SH)	77.9	NA	6	4	Symptoms (4-point scale),* OSS, TBUT, and AE
Park DH, 2016[e6]	Korea	RCT	Single-center	63	Postcataract surgery	3% DQ	AT (0.1% SH)	54	0	6	12	OSDI, ST, OSS, TBUT, HOA, and AE
Cui, 2018[e7]	Korea	RCT	Single-center	94	Postcataract surgery	3% DQ	AT (0.1% SH)	63.8	0	4	12	OSDI, OSS, TBUT, ST, HOA, IC, and TCR
Inoue, 2017[e8]	Japan	RCT	Single-center	42	Postcataract surgery	3% DQ	AT (Mytear)	59.9	NA	6	4	OSS, TBUT, and HOA
Miyake, 2017[e9]	Japan	RCT	Multicenter	154	Postcataract surgery	3% DQ	AT (unspecified)	65.8	NA	6	4	Symptoms (4-point scale), OSS, and TBUT
Shimazaki–Den, 2013[e10]	Japan	RCT	Multicenter	17	STBUT	3% DQ	AT (Soft Santear)	88.2	NA	6	4	Symptoms (4-point scale), OSS, and * TBUT
Kaido, 2018[e11]	Japan	RCT	Single-center	27	STBUT	3% DQ	AT (Soft Santear)	70.4	NA	6	5	Symptoms (4-point scale), OSS, TBUT, TMH, and CS
Matsumoto, 2012[e12]	Japan	RCT	Multicenter	190	NA	1% DQ,†; 3% DQ	Placebo	80.5	23.1	6	6	Symptoms (4-point scale), OSS, TBUT, and AE
Hwang, 2014[e13]	Korea	RCT	Single-center	150	ADDE	3% DQ; 3% DQ + AT	AT (0.1% SH)	78.7	NA	4	12	OSDI, OSS, TBUT, ST, IC, and AE
Kim, 2017[e14]	Korea	RCT	Single-center	96	EDED	3% DQ + AT‡	AT (0.15% SH + LPO)	79.2	0	4	12	OSDI, OSS, TBUT, ST, TMH, AE
Jun, 2019[e15]	Korea	RCT	Single-center	117	Postcataract surgery	3% DQ; 3% DQ (PF)	AT (0.15% SH)	64.1	NA	6	12	OSDI, OSS, TBUT, ST, and meibum quality and expressibility
Toda, 2014[e16]	Japan	RCT	Multicenter	105	Post-LASIK	3% DQ; 3% DQ + AT	AT‡ (0.3% SH, Soft Santear)	61.9	NA	6	4	Symptoms (4-point scale), OSS, TBUT, and ST
Kinoshita, 2012[e17]	Japan	RCT	Multicenter	205	Not respond to AT	1% RB†; 2% RB	AT (Soft Santear)	85.8	15.1	4	4	Symptoms (4-point scale), OSS, TBUT, ST, and AE
Kinoshita, 2013[e18]	Japan	RCT	Multicenter	188	Not respond to AT	2% RB	AT (0.1% SH)	86.7	18.1	4 versus 6	4	Symptoms (4-point scale), OSS, TBUT, ST, and AE
Igarashi, 2015[e19]	Japan	RCT	Multicenter	25	Post-LASIK or ReLex	2% RB	AT (unspecified)	88	0	4	4	Symptoms (4-point scale), OSS, TBUT, ST, and AE
Kobashi, 2017[e20]	Japan	RCT	Single-center	40	Post-PKP	2% RB	3% DQ	47.5	0	4	4	DEQS, OSS, and TBUT
Shimazaki, 2017[e21]	Japan	RCT	Multicenter	67	Office workers	2% RB	3% DQ	70.1	NA	4 versus 6	4	DEQS, OSS, TBUT, and AE
Nebbioso, 2013[e22]	Italy	RCT	Multicenter	40	Glaucoma	ED	Placebo	80	NA	3	2	OSDI, TBUT, ST, and OPI
Meerovitch, 2013[e23]	United States	RCT	Multicenter	150	NA	1% MIM-D3†; 5% MIM-D3	Placebo	75.3	0	2	6	OSDI, OSS, and AE

(*Continued*)

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TABLE 1. (*Continued*) Characteristics of 39 Included RCTs

Author, Year	Country	Study Design	Multicenter/ Single-center	No. of Patients	Specific Condition	Intervention	Comparator	Female (%)	SS (%)	Dosage (times/d)	Follow-up (wk)	Reported Outcomes
NCT03019627[e24]	United States	RCT	Single-center	150	NA	rhNGF	Placebo	87.3	NA	6	12	SANDE, OSS, TBUT, CS, and AE
NCT03982368[e25]	Italy	RCT	Single-center	170	Postcataract/ refractive surgery	rhNGF	Placebo	59.8	NA	6	12	SANDE, OSS, TBUT, CS, and AE
Tananuvat, 2001[e26]	United States	Paired-eye RCT	Single-center	12	NA	20% AS§	Placebo§	58.3	41.7	6	8	Symptoms (4-point scale),* OSS,* TBUT,* ST, and * AE
Kojima, 2005[e27]	Japan	RCT	Single-center	20	NA	20% AS	AT (Soft Santear)	80	85	6	2	VAS, OSS, TBUT, and ST
Noda–Tsuruya, 2006[e28]	Japan	RCT	Multicenter	27	Post-LASIK	20% AS	AT (Soft Santear)	0	NA	5	12	Symptoms (5-point scale), OSS, TBUT, and ST II
Urzua, 2012[e29]	Chile	CORCT	Single-center	12	NA	20% AS	AT (Systane)	91.7	0	4	2	OSDI, OSS, and TBUT
Celebi, 2014[e30]	Turkey	CORCT	Single-center	20	NA	20% AS	AT (Refresh)	90	NA	4	4	OSDI, OSS, TBUT, ST, and AE
Yilmaz, 2017[e31]	Turkey	CORCT	Single-center	24	Isotretinoin	40% AS	AT (unspecified)	83.3	NA	NA	4	OSDI, TBUT, and ST
Noble, 2004[e32]	United Kingdom	CORCT	Single-center	16	NA	50% AS	AT (mixed types)	56	37.5	Vary	4	VAS,* OSS, and IC
Mukhopadhyay, 2015[e33]	India	RCT	Single-center	144	Hansen disease	20% CBS; 20% AS	AT (unspecified)	NA	NA	6	12	McMonnies score, OSS, TBUT, ST, IC, and protein in tear
Campos, 2019[e34]	Italy	CORCT	Multicenter	60	NA	20% CBS	20% AS	73.3	26.7	8	4	OSDI, OSS, TBUT, ST, and AE
Fea, 2016[e35]	Italy	RCT	Single-center	30	SS	APL	AT (0.2% SH)	96.7	100	4	12	OSDI, OSS, TBUT, ST, IVCM, AE, and OPI
Garcia–Conca, 2019[e36]	Spain	RCT	Single-center	83	NA	PRP	AT (0.18% SH)	96.4	NA	6	4	OSDI, OSS, TBUT, ST, and tear osmolarity
Ji, 2019[e37]	Korea	RCT	Multicenter	18	NA	0.05% CSA	3% DQ	55.5	NA	2 versus 6	4	OSDI, OSS, TBUT, ST
Park CH, 2019[e38]	Korea	RCT	Multicenter	115	NA	0.05% CSA + AT†; 0.05% nCSA + AT	3% DQ	66.7	0	2 + 4 versus 6	12	OSDI, OSS, TBUT, ST, and AE
Patil, 2018[e39]	India	RCT	Single-center	80	NA	0.1% CSA + AT (1% MC)	2% RB + AT (1% MC)	25	0	NA	12	OSDI, TBUT, and ST

*Insufficient data for pooling.
†Omitted.
‡Two arms of different types of artificial tears.
§Allow other cointerventions to be used.

ADDE, aqueous deficient dry eye; AE, adverse event; AT, artificial tear; CORCT, crossover randomized controlled trial; CS, corneal sensation; DQ, diquafosol; DEQS, Dry Eye–Related Quality-of-Life Score; ED, eledoisin; EDED, evaporative dry eye; HOA, higher order aberrations; IC, impression cytology; IVCM, in vivo confocal microscopy; LASIK, laser-assisted in situ keratomileusis; LPO, carbomer-based lipid-containing artificial tear (Liposic EDO); MC, methyl cellulose; NA, data not available; nCSA, cyclosporine nanoemulsion; OPI, ocular protection index; OSS, ocular surface staining; PF, preservative free; PKP, penetrating keratoplasty; RB, rebamipide; ReLex, refractive lenticule extraction; SANDE, Symptom Assessment Questionnaire in Dry Eye; SH, sodium hyaluronic acid; SS, Sjögren's syndrome; STBUT, short tear break-up time; TCR, tear clearance rate; TMH, tear meniscus height; VAS, visual analog scale.

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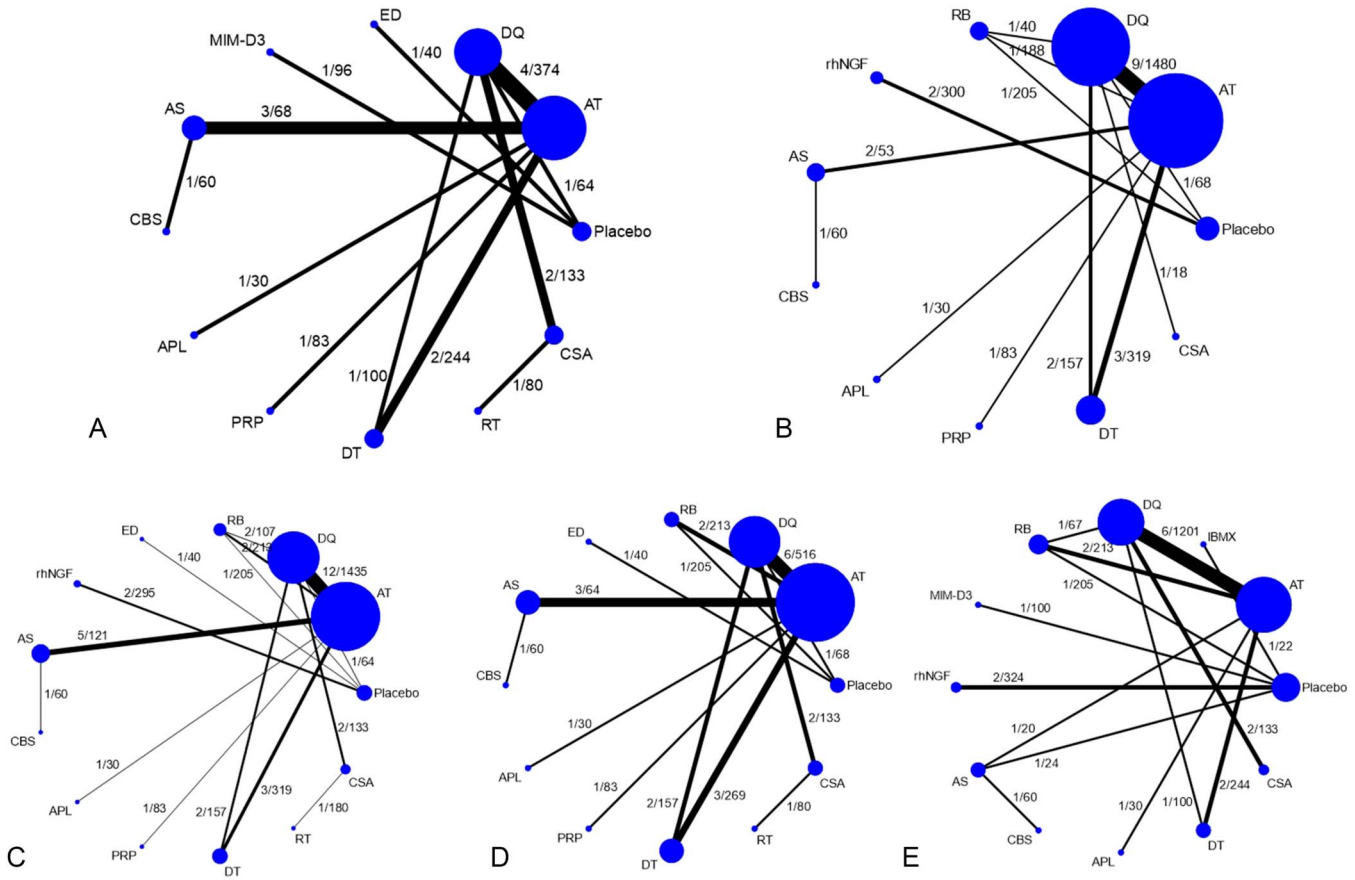

FIGURE 2. Network maps of primary and secondary outcomes. Nodes and lines represent interventions and direct comparisons with weighted size according to the number of studies for each direct comparison. The numbers on the lines indicate the number of studies/participants for each comparison: (A) OSDI, (B) corneal fluorescein staining, (C) TBUT, (D) ST, and (E) adverse events. AT, artificial tears; DQ, diquafosol; ED, eledoisin; NA, data not available; RB, rebamipide. (The full color version of this figure is available at www.corneajrnl.com.)

USMDs of −2.81 [95% confidence interval (CI): −4.00 to −1.63; $I^2 = 20\%$], −10.62 (−17.86 to −3.39; $I^2 = 83.7\%$), and −5.21 (−7.09 to −3.33; $I^2 = 0\%$), respectively (Appendix 5, Supplemental Digital Content 1, http://links.lww.com/ICO/B328). High heterogeneity was observed for AS versus artificial tears comparisons possibly because a consequence of 1 study[e31] including only patients with isotretinoin-related DED. A sensitivity analysis removing this study reduced the I^2 value to 38.8% with a higher USMD of −13.98 (−19.56 to −8.40).

Network Meta-analysis

Seventeen studies (1178 patients, Appendix 4, Supplemental Digital Content 1, http://links.lww.com/ICO/B328) representing 12 interventions (artificial tears, placebo, diquafosol, eledoisin, MIM-D3, AS, CBS, APL, PRP, DT, RT, and CSA) were analyzed (Fig. 2A) with no evidence of inconsistency ($\chi^2 = 1.52$, $P = 0.84$). Corresponding to the results of the direct meta-analysis, OSDI scores significantly reduced in 6 interventions compared with artificial tears—diquafosol, AS, CBS, APL, PRP, and DT with USMDs (95% CI) of −3.67 (−6.65 to −0.70), −9.76 (−14.04 to −5.49), −16.76 (−27.40 to −6.13), −31.85 (−43.19 to −20.51), −19.3 (−26.32 to −12.28), and −5.82 (−9.59 to −2.05), respectively (Table 2). Among topical secretagogues and their combinations, eledoisin, RT, and DT seemed to reduce OSDI scores greater than diquafosol, but these were not significant. For biological tear substitutes, APL and PRP significantly reduced OSDI scores compared with AS. The top 4 ranked interventions according to SUCRA were APL (99.4%), PRP (87.3%), CBS (81.9%), and AS (66%) (Appendix 4, Supplemental Digital Content 1, http://links.lww.com/ICO/B328).

All 66 pairwise comparisons in NMA were mostly downgraded as low certainty of evidence because of study limitation (100%), indirectness (62.1%), inconsistency (89.4%), and imprecision (59.1%) (Appendix 6, Supplemental Digital Content 1, http://links.lww.com/ICO/B328).

Ocular Surface Staining

Thirty-six studies reported ocular surface staining using various methods of measurement. There was a huge variety of types of dyes used for ocular surface staining, area of

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TABLE 2. Estimation of the Relative Treatment Effects (95% CIs) With Ocular Surface Disease Index Scores in the Upper Triangle and Corneal Fluorescein Staining in the Lower Triangle by Treatments

AT	1.82 (−4.13 to 7.77)	−3.67* (−6.65 to −0.70)	−9.18 (−19.06 to 0.69)	1.60 (−6.14 to 9.35)	−9.77* (−14.04 to −5.49)	−16.76* (−27.40 to −6.13)	−31.85* (−43.19 to −20.51)	−19.30* (−26.32 to −12.28)	−5.82* (−9.59 to −2.06)	−6.01 (−16.17 to 4.14)	−1.10 (−9.55 to 7.34)
−0.71* (−1.18 to −0.25)	**Placebo**	−5.49* (−10.65 to −0.33)	−11.00* (−18.88 to −3.12)	−0.21 (−5.19 to 4.76)	−11.58* (−18.79 to −4.38)	−18.58* (−30.69 to −6.47)	−33.67* (−46.48 to −20.86)	−21.12* (−30.32 to −11.91)	−7.64* (−14.31 to −0.97)	−7.83 (−18.82 to 3.15)	−2.92 (−12.35 to 6.50)
0.20* (0.02 to 0.37)	0.91* (0.45 to 1.37)	**DQ**	−5.51 (−14.93 to 3.91)	5.28 (−1.88 to 12.44)	−6.09* (−11.14 to −1.05)	−13.09* (−24.06 to −2.13)	−28.18* (−39.90 to −16.45)	−15.63* (−23.25 to −8.00)	−2.15 (−6.39 to 2.09)	−2.34 (−12.04 to 7.36)	2.57 (−5.32 to 10.46)
0.30 (−0.08 to 0.67)	1.01* (0.60 to 1.43)	0.10 (−0.28 to 0.48)	**ED** / **RB**	10.79* (1.46 to 20.11)	−0.58 (−11.26 to 10.10)	−7.58 (−22.03 to 6.87)	−22.67* (−37.71 to −7.63)	−10.12 (−22.24 to 2.00)	3.36 (−6.97 to 13.69)	3.17 (−10.35 to 16.69)	8.08 (−4.21 to 20.36)
−0.75* (−1.35 to −0.15)	−0.04 (−0.41 to 0.34)	−0.95* (−1.54 to −0.35)	−1.05* (−1.60 to −0.49)	**MIM-D3** / **rhNGF**	−11.37* (−20.12 to −2.62)	−18.37* (−31.46 to −5.28)	−33.45* (−47.19 to −19.72)	−20.90* (−31.36 to −10.45)	−7.43 (−15.74 to 0.89)	−7.62 (−19.67 to 4.44)	−2.71 (−13.36 to 7.94)
−0.07 (−0.68 to 0.55)	0.65 (−0.13 to 1.42)	−0.26 (−0.90 to 0.38)	−0.36 (−1.08 to 0.36)	0.68 (−0.18 to 1.54)	**AS**	−7.00 (−16.73 to 2.74)	−22.08* (−34.21 to −9.96)	−9.53* (−17.76 to −1.31)	3.94 (−1.71 to 9.59)	3.75 (−7.17 to 14.67)	8.66 (−0.69 to 18.01)
1.08* (0.16 to 2.00)	1.79* (0.76 to 2.82)	0.88 (−0.05 to 1.82)	0.78 (−0.21 to 1.77)	1.83* (0.74 to 2.92)	1.15* (0.47 to 1.82)	**CBS**	−15.09 (−30.63 to 0.46)	−2.54 (−15.28 to 10.21)	10.94 (−0.31 to 22.20)	10.75 (−3.88 to 25.38)	15.66* (2.16 to 29.16)
1.31* (0.39 to 2.24)	2.03* (0.99 to 3.07)	1.12* (0.18 to 2.06)	1.02* (0.02 to 2.02)	2.06* (0.96 to 3.17)	1.38* (0.27 to 2.49)	0.23 (−1.07 to 1.54)	**APL**	12.55 (−0.79 to 25.89)	26.03* (14.07 to 37.98)	25.84* (10.61 to 41.06)	30.75* (16.60 to 44.89)
2.52* (1.82 to 3.23)	3.24* (2.39 to 4.08)	2.33* (1.60 to 3.05)	2.23* (1.43 to 3.02)	3.27* (2.35 to 4.20)	2.59* (1.65 to 3.53)	1.44* (0.29 to 2.60)	1.21* (0.04 to 2.37)	**PRP**	13.48* (5.51 to 21.45)	13.29* (0.94 to 25.63)	18.20* (7.21 to 29.18)
0.18 (−0.13 to 0.48)	0.89* (0.34 to 1.44)	−0.02 (−0.34 to 0.30)	−0.12 (−0.60 to 0.35)	0.93* (0.26 to 1.59)	0.24 (−0.45 to 0.93)	−0.90 (−1.87 to 0.06)	−1.14* (−2.12 to −0.16)	−2.35* (−3.12 to −1.58)	**DT**	−0.19 (−10.79 to 10.40)	4.72 (−4.25 to 13.68)
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**RT**	4.91 (−0.74 to 10.56)
0.62 (−0.41 to 1.66)	1.34* (0.22 to 2.45)	0.43 (−0.59 to 1.45)	0.33 (−0.76 to 1.41)	1.37* (0.20 to 2.55)	0.69 (−0.51 to 1.89)	−0.46 (−1.84 to 0.92)	−0.69 (−2.08 to 0.70)	−1.90* (−3.15 to −0.65)	0.45 (−0.62 to 1.52)	NA	**CSA**

Mean difference < 0 favors drug in the column of upper triangle, mean difference > 0 favors drug in the row of lower triangle.
*Statistical significance.
AT, artificial tears; DQ, diquafosol; ED, eledoisin; NA, data not available; RB, rebamipide.

assessment, and grading scales. Fluorescein was the most frequently used dye (33 studies, 91.7%), followed by rose bengal (10 studies, 27.8%) and lissamine green (7 studies, 19.4%). Among studies using fluorescein, 22 studies (66.7%) assessed only corneal damage, whereas 11 studies (33.3%) assessed both corneal and conjunctival damage. Given these heterogeneous data and cornea being the most clinically important and the most common evaluated area, we decided to focus on the studies which reported only corneal fluorescein staining (22 studies). These studies reported in 5 grading scales: the National Eye Institute (8 studies), Shimmura scale (8 studies), Oxford scale (4 studies), Miyata scale (1 study), and Toda scale (1 study). Lower scores represented more favorable outcomes.

Direct Meta-analysis

Five comparisons contained sufficient data for pooling: diquafosol versus artificial tears (N/n = 9/1480), AS versus artificial tears (N/n = 2/53), DT versus artificial tears (N/n = 3/319), DT versus diquafosol (N/n = 2/157), and rhNGF versus placebo (N/n = 2/300) (Appendix 7, Supplemental Digital Content 1, http://links.lww.com/ICO/B328). Diquafosol significantly decreased corneal fluorescein staining scores compared with artificial tears, with SMD of −0.21 (95% CI: −0.37 to −0.05; I^2 = 51.3%). A sensitivity analysis pooling only studies with the Shimmura scale decreased the I^2 value to 33.4% with a USMD of −0.20 (−0.39 to −0.02), indicating that different measurement scales could partially cause high heterogeneity, although the magnitude of pooled effect size was unchanged (Appendix 5, Supplemental Digital Content 1, http://links.lww.com/ICO/B328).

Network Meta-analysis

Twenty-two studies (2680 patients, Appendix 7, Supplemental Digital Content 1, http://links.lww.com/ICO/B328) with 11 interventions (placebo, artificial tears, diquafosol, rebamipide, rhNGF, AS, CBS, APL, PRP, DT, and CSA) were mapped (Fig. 2B) without evidence of inconsistency from the global test (χ^2 = 0.75, P = 0.94). PRP, APL, CBS, and diquafosol significantly reduced corneal fluorescein staining compared with artificial tears with SMDs of −2.52 (95% CI: −3.23 to −1.82), −1.31 (−2.24 to −0.39), −1.08 (−2.00 to −0.16), and −0.20 (−0.37 to −0.02), respectively (Table 2). RhNGF was found to have significant higher staining scores than artificial tears (SMD 0.75; 0.15–1.35). Among topical secretagogues, diquafosol, rebamipide, and DT significantly reduced corneal fluorescein staining compared with rhNGF. PRP and APL significantly decreased corneal fluorescein staining more than AS, topical secretagogues, and DT (Table 2). The top 3 ranked treatments were PRP (99.7%), APL (84.5%), and CBS (79.9%) (Appendix 7, Supplemental Digital Content 1, http://links.lww.com/ICO/B328).

Of 55 pairwise comparisons, most of them were downgraded as low certainty of evidence because of study limitation (98.2%), indirectness (76.4%), inconsistency (89.4%), and imprecision (16.4%) (Appendix 8, Supplemental Digital Content 1, http://links.lww.com/ICO/B328).

Tear Break-up Time

Thirty-four studies (3167 patients) reported TBUT. Higher scores indicated better outcomes.

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Direct Meta-analysis

Eight treatment comparisons were available for analysis. The most common comparison was diquafosol versus artificial tears (N/n = 12/1403), followed by AS versus artificial tears (N/n = 6/330) and DT versus artificial tears (N/n = 3/319) (Appendix 9, Supplemental Digital Content 1, http://links.lww.com/ICO/B328). Diquafosol slightly increased TBUT compared with artificial tears, with a USMD of 0.61 (95% CI: 0.28–0.94, I^2 = 60.5%). After subgroup analysis by disease severity, diquafosol significantly increased TBUT in mild-to-moderate DED (2.36; 1.39–3.34, I^2 = 0%), whereas decreased TBUT in moderate-to-severe DED (0.25; 0.22–0.28, I^2 = 0%) compared with artificial tears. AS significantly improved TBUT compared with artificial tears with a USMD of 3.41 (1.32–5.49, I^2 = 92.0%) (Appendix 5, Supplemental Digital Content 1, http://links.lww.com/ICO/B328). A sensitivity analysis excluding 3 studies[e28,e31,e33] which examined patients with specific conditions (postlaser-assisted in situ keratomileusis dry eye, isotretinoin-related DED, and Hansen disease, respectively), resulted in a decrease of I^2 statistic to 0%. The effect size decreased to 1.24 (0.39–2.09). DT also significantly increased TBUT compared with artificial tears, with a USMD of 0.43 (0.14–0.72, I^2 = 0%).

Network Meta-analysis

Thirty-four studies with 13 interventions (placebo, artificial tears, diquafosol, rebamipide, eledoisin, rhNGF, AS, CBS, APL, PRP, DT, RT, and CSA) were pooled with evidence of inconsistency (χ^2 = 67.91, $P < 0.001$). Loop-specific approaches identified 2 loops (artificial tears–AS–CBS and placebo–diquafosol–rebamipide) with high IF (10.69 and 2.45). Artificial tears–AS comparisons contributed substantially to inconsistency of the loop. A study[e33] in patients with Hansen disease was identified as the source of inconsistency. A sensitivity analysis excluding this particular study resulted in an improvement in the global test value (χ^2 = 3.41, P = 0.49). The final network of 33 studies (3025 patients, Fig. 2C) was performed. Diquafosol, AS, CBS, and RT significantly increased TBUT compared with artificial tears with USMDs of 0.73 (95% CI: 0.27–1.17), 2.17 (1.30–3.04), 2.67 (0.53–4.82), and 2.46 (0.36–4.55), respectively (Table 3). Meanwhile, eledoisin showed a significantly shorter TBUT than artificial tears, with a USMD of −2.85 (−5.01 to −0.68). Among topical secretagogues and their combinations, RT, DT, rebamipide, and diquafosol significantly increased TBUT compared with eledoisin. For biological tear substitutes, only AS significantly increased TBUT compared with PRP. Based on SUCRA, the top 3 ranked interventions were CBS (89.1%), RT (88.6%), and AS (87.3%) (Appendix 10, Supplemental Digital Content 1, http://links.lww.com/ICO/B328).

Schirmer Test

Twenty-three studies reported Schirmer scores. One study performed the Schirmer II test and was excluded from analysis. Twenty-two studies (N/n = 22/1741) with the Schirmer I test were pooled (Appendix 9, Supplemental Digital Content 1, http://links.lww.com/ICO/B328). Higher scores indicated better outcomes.

Direct Meta-analysis

Seven comparisons contained sufficient data for pooling: diquafosol versus artificial tears (N/n = 6/516), rebamipide versus artificial tears (N/n = 2/213), AS versus artificial tears (N/n = 4/160), DT versus artificial tears (N/n = 3/269), DT versus diquafosol (N/n = 2/157), CSA versus diquafosol (N/n = 2/133), and CBS versus AS (N/n = 2/160). Only

TABLE 3. Estimation of Relative Treatment Effects (95% CIs) of TBUT in the Upper Triangle and ST in the Lower Triangle by Treatments

AT	-0.55 (-1.92,0.82)	0.73* (0.27,1.20)	0.63 (-0.21,1.46)	-2.85* (-5.01,-0.68)	-0.95 (-2.70,0.81)	2.17* (1.30,3.05)	2.67* (0.53,4.82)	1.50 (-0.07,3.07)	0.35 (-1.14,1.84)	0.54 (-0.27,1.35)	2.46* (0.36,4.55)	0.88 (-0.30,2.05)
0.92 (-0.45,2.29)	**Placebo**	1.28 (-0.09,2.64)	1.17 (-0.08,2.43)	-2.30* (-3.98,-0.62)	-0.40 (-1.49,0.69)	2.72* (1.11,4.33)	3.22* (0.68,5.76)	2.05 (-0.03,4.13)	0.90 (-1.13,2.92)	1.09 (-0.48,2.66)	3.00* (0.54,5.47)	1.42 (-0.32,3.17)
-0.57 (-1.42,0.27)	-1.49* (-2.91,-0.08)	**DQ**	-0.11 (-0.96,0.75)	-3.58* (-5.74,-1.41)	-1.68 (-3.43,0.07)	1.44* (0.45,2.44)	1.94 (-0.26,4.14)	0.77 (-0.86,2.40)	-0.38 (-1.94,1.18)	-0.19 (-1.05,0.67)	1.73 (-0.32,3.77)	0.15 (-0.93,1.22)
0.52 (-0.58,1.62)	-0.40 (-1.51,0.71)	1.09 (-0.18,2.37)	**RB**	-3.47* (-5.57,-1.38)	-1.57 (-3.23,0.09)	1.55* (0.34,2.76)	2.05 (-0.26,4.35)	0.87 (-0.90,2.65)	-0.28 (-1.98,1.43)	-0.08 (-1.22,1.05)	1.83 (-0.38,4.05)	0.25 (-1.13,1.63)
-2.28* (-4.42,-0.14)	-3.20* (-4.85,-1.55)	-1.71 (-3.87,0.46)	-2.80* (-4.78,-0.81)	**ED**	1.90 (-0.10,3.90)	5.02* (2.69,7.35)	5.52* (2.47,8.56)	4.35* (1.67,7.02)	3.20* (0.57,5.82)	3.39* (1.09,5.69)	5.30* (2.32,8.28)	3.72* (1.30,6.15)
NA	NA	NA	NA	NA	**rhNGF**	3.12* (1.17,5.07)	3.62* (0.85,6.39)	2.45* (0.10,4.80)	1.30 (-1.00,3.59)	1.49 (-0.42,3.40)	3.40* (0.71,6.10)	1.82 (-0.24,3.88)
-0.04 (-1.02,0.94)	-0.96 (-2.64,0.72)	0.53 (-0.75,1.82)	-0.56 (-2.03,0.91)	2.24 (-0.11,4.59)	NA	**AS**	0.50 (-1.46,2.46)	-0.67 (-2.47,1.12)	-1.82* (-3.55,-0.10)	-1.63 (-2.83,-0.44)	0.28 (-1.99,2.56)	-1.30 (-2.77,0.18)
-0.04 (-2.49,2.42)	-0.96 (-3.77,1.85)	0.53 (-2.06,3.13)	-0.56 (-3.25,2.13)	2.24 (-1.02,5.50)	NA	0.00 (-2.25,2.25)	**CBS**	-1.17 (-3.83,1.48)	-2.32 (-4.94,0.29)	-2.13 (-4.43,0.17)	-0.22 (-3.22,2.79)	-1.80 (-4.25,0.66)
0.00 (-1.08,1.08)	-0.92 (-2.67,0.82)	0.57 (-0.80,1.94)	-0.52 (-2.06,1.02)	2.28 (-0.12,4.68)	NA	0.04 (-1.42,1.50)	0.04 (-2.65,2.72)	**APL**	-1.15 (-3.31,1.01)	-0.96 (-2.72,0.81)	0.96 (-1.66,3.57)	-0.62 (-2.58,1.34)
-1.50* (-2.70,-0.30)	-2.42* (-4.25,-0.60)	-0.93 (-2.40,0.54)	-2.02* (-3.65,-0.39)	0.78 (-1.68,3.24)	NA	-1.46 (-3.01,0.09)	-1.46 (-4.20,1.27)	-1.50 (-3.12,0.12)	**PRP**	0.19 (-1.50,1.89)	2.11 (-0.46,4.68)	0.53 (-1.37,2.42)
-0.29 (-1.49,0.90)	-1.21 (-3.02,0.59)	0.28 (-1.11,1.67)	-0.81 (-2.43,0.81)	1.99 (-0.46,4.43)	NA	-0.26 (-1.83,1.32)	-0.26 (-3.01,2.50)	-0.29 (-1.90,1.32)	1.21 (-0.49,2.90)	**DT**	1.91 (-0.30,4.13)	0.33 (-1.04,1.71)
-1.85 (-4.11,0.40)	-2.78* (-5.30,-0.25)	-1.28 (-3.38,0.82)	-2.37 (-4.83,0.08)	0.42 (-2.59,3.44)	NA	-1.82 (-4.28,0.64)	-1.82 (-5.15,1.52)	-1.85 (-4.36,0.65)	-0.35 (-2.91,2.20)	-1.56 (-4.03,0.91)	**RT**	-1.58 (-3.31,0.15)
-0.27 (-1.98,1.43)	-1.20 (-3.25,0.86)	0.30 (-1.20,1.79)	-0.79 (-2.75,1.17)	2.00 (-0.63,4.64)	NA	-0.24 (-2.21,1.74)	-0.24 (-3.23,2.76)	-0.27 (-2.30,1.75)	1.23 (-0.86,3.32)	0.02 (-1.97,2.00)	1.58 (0.11,3.05)	**CSA**

Mean difference > 0 favors drug in the column of upper triangle, mean difference < 0 favors drug in the row of lower triangle.
*Statistical significance.AT, artificial tears; DQ, diquafosol; ED, eledoisin; NA, data not available; RB, rebamipide.

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diquafosol significantly increased Schirmer scores compared with artificial tears, with a USMD of 0.94 (95% CI: 0.16–1.72, I^2 = 0%). Other comparisons were not significantly different (Appendix 5, Supplemental Digital Content 1, http://links.lww.com/ICO/B328).

Network Meta-analysis

The network contained 22 studies with 12 interventions (placebo, artificial tears, diquafosol, rebamipide, eledoisin, AS, CBS, APL, PRP, DT, RT, and CSA). The consistency assumption did not hold (χ^2 = 57.01, $P < 0.001$), and the loop-specific approach identified the artificial tears–AS–CBS loop as having a high IF of 6.70. After excluding a study[e33] comparing artificial tears, AS, and CBS, the consistency assumption of the network was hold (χ^2 = 6.92, P = 0.075). The final network of 21 studies (1597 patients, Fig. 2D) showed that eledoisin and PRP significantly increased Schirmer scores compared with artificial tears, with USMDs of 2.28 (95% CI: 0.14–4.42) and 1.5 (0.30–2.70), respectively (Table 3). Among topical secretagogues, only eledoisin significantly increased ST compared with diquafosol (2.80; 0.81–4.78). SUCRA suggested that the top ranked intervention was eledoisin (91.1%), followed by RT (84.9%) and PRP (81.9%) (Appendix 10, Supplemental Digital Content 1, http://links.lww.com/ICO/B328).

Summary of Treatment Effectiveness

In the summary of treatment effectiveness, 4 main outcomes (OSDI, corneal fluorescein staining, TBUT, and ST) were considered simultaneously. A 2-way-scatter plot was constructed with SUCRAs of OSDI scores on the *x* axis and corneal fluorescein staining, TBUT, and ST on the *y* axis (Fig. 3). All interventions were considered, except rebamipide, MIM-D3 (no data on OSDI), and rhNGF (no data on TBUT, corneal fluorescein staining, and ST). The interventions falling in the right upper quadrant indicated the best treatment. Biological tear substitutes, which were APL, PRP, CBS, and to a lesser extent AS, were the most effective interventions, followed by the combinations of topical secretagogues and artificial tears (RT and DT) and monotherapy of topical secretagogues (eledoisin and diquafosol).

Adverse Events

Twenty-one studies reported ocular adverse events such as eye discomfort, eye irritation, and eye discharge (Appendix 11, Supplemental Digital Content 1, http://links.lww.com/ICO/B328). Most of them were mild and not sight-threatening events. From direct meta-analysis, only diquafosol significantly increased ocular adverse events compared with artificial tears, with the risk ratio of 1.64 (95% CI: 1.10–2.46; I^2 = 0%) (Appendix 5, Supplemental Digital Content 1, http://links.lww.com/ICO/B328). NMA of 21 studies (2538 patients) with 12 interventions (placebo, artificial tears, IBMX, diquafosol, rebamipide, MIM-D3, rhNGF, AS, CBS, APL, DT, and CSA; Fig. 2D) revealed that both topical secretagogues (ie, IBMX, diquafosol, MIM-D3, and rhNGF) and biological tear substitutes (ie, AS, CBS, and APL) were likely to produce ocular adverse events compared with artificial tears, but not statistically significant (Appendix 12, Supplemental Digital Content 1, http://links.lww.com/ICO/B328).

FIGURE 3. Scatter plot of surface under cumulative ranking curves of multiple outcomes. Triangles, circles, and diamonds represent the SUCRA values of all objective outcomes; corneal FS staining, TBUT, and ST of each intervention. The position of each dot indicates the relationship among SUCRA values of those outcomes in the Y-axis and SUCRA values of OSDI in the X-axis. The higher SUCRA value suggests more favorable outcome. The interventions falling in the right upper quadrant indicate the best treatment. AT, artificial tears; DQ, diquafosol; ED, eledoisin; FS, fluorescein; RB, rebamipide. (The full color version of this figure is available at www.corneajrnl.com.)

Clustered rank plots suggested that all interventions had similar ocular adverse events. Meanwhile, both biological tear substitutes and topical secretagogues had superior short-term efficacies compared with artificial tears and placebo (Fig. 4).

Transitivity Assessment

We observed heterogeneity in some effect modifiers, including age, sex, dry eye etiology, and severity of DED. Transitivity could be partially assessed because of inconsistent reports of effect modifiers across all included RCTs, as shown in Appendix 13 (Supplemental Digital Content 1, http://links.lww.com/ICO/B328). Both partial assessment and intransitivity found in our NMA were thoroughly addressed and resulted in downgrading the certainty of network estimates in 2 primary outcomes (dry eye symptom scores and ocular surface staining).

Publication Bias

No evidence of asymmetry in comparison-adjusted funnel plots was identified in the 5 networks, corresponding to the results from the Egger test (Appendix 14, Supplemental Digital Content 1, http://links.lww.com/ICO/B328).

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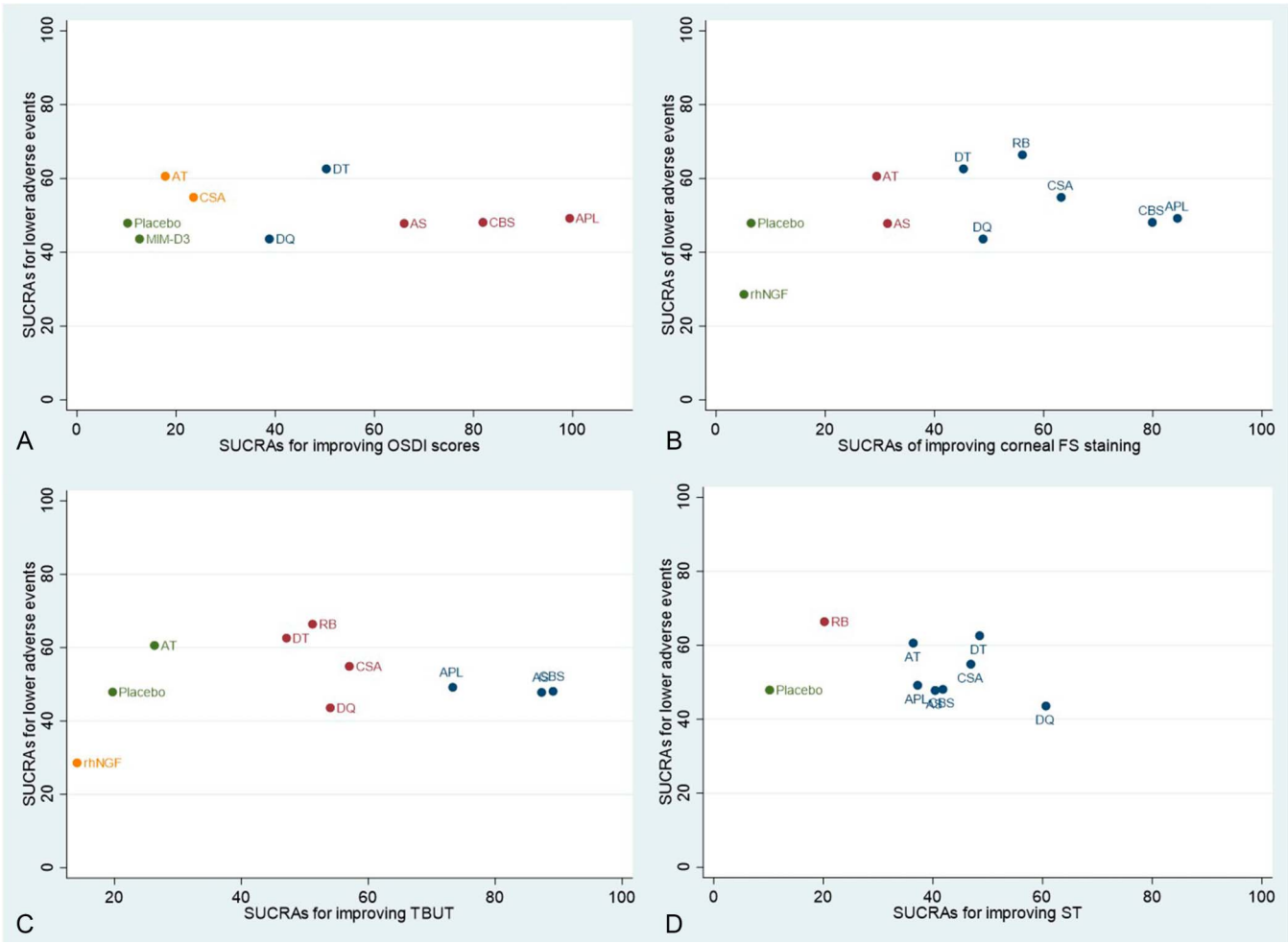

FIGURE 4. Clustered ranking plot of topical secretagogues, biological tear substitutes and their comparisons showing the SUCRAs for lowest probability of ocular adverse events (AEs) versus the SUCRAs for highest probability of improving treatment outcomes. A, OSDI, (B) corneal FS staining, (C) TBUT, and (D) ST. Each symbol represents a group of interventions in each cluster. Interventions lying in the right upper corner are associated with higher probability of treatment efficacy and lower probability of AEs. AT, artificial tears; DQ, diquafosol; FS, fluorescein; RB, rebamipide. (The full color version of this figure is available at www.corneajrnl.com.)

DISCUSSION

We had performed a NMA including 39 RCTs to compare efficacy among biological tear substitutes and topical secretagogues in DED treatment. The results from our NMA suggested that biological tear substitutes generally outperformed topical secretagogues, artificial tears, and a combination of topical secretagogue and artificial tears, leading to a marked improvement in the corneal fluorescein staining and TBUT and a reduction in OSDI scores. The risk of ocular adverse events was not significantly different among various types of biological tear substitutes and topical secretagogues.

For OSDI scores, APL, PRP, CBS, and AS were the 4 highest ranked interventions. A relative treatment effect of OSDI scores in those interventions compared with artificial tears was at or higher than the minimally clinically important difference,[33] highlighting their efficacy for relieving dry eye symptoms. Our findings were consistent with previous systematic reviews and meta-analyses which showed short-term benefits of AS in reducing dry eye symptoms compared with control.[10,11,13] Biological tear substitutes can provide a diversity of bioactive ingredients that are missing from simple artificial tears. AS, the most common formulation, contains high levels of proteins and cellular growth factors (eg, epidermal growth factor, nerve growth factor, insulin-liked growth factor, and platelet-derived growth factor), which are necessary for corneal epithelial healing.[34] Platelet-derived eye drops (APL and PRP) and CBS contain larger amounts of epidermal growth factor, platelet-derived growth factor, and transforming growth factor beta compared with AS.[34–37] These considerably higher levels of growth factors may contribute to better dry eye symptom relief and corneal epithelial healing compared with AS. This hypothesis is supported by our NMA results that PRP, APL, and CBS had superior efficacy over AS in improving OSDI scores and corneal fluorescein staining. In addition, treatment with biological tear substitutes resulted in a significant

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improvement of TBUT, similar to previous findings from a meta-analysis of AS.[12] However, there remain some concerns about their clinical usefulness, including unstandardized preparation protocols, blood donation, requirement for cold storage, contraindications (eg, children, blood-transmitted infectious carriers, and severe anemia), and high cost.[34]

A previous meta-analysis in Asian population[9] demonstrated that diquafosol significantly improved ocular fluorescein staining, TBUT, and ST compared with artificial tears, corresponding to our results. We also found that diquafosol increased TBUT in patients with mild-to-moderate DED more than those with moderate-to-severe DED. The combination of diquafosol and artificial tears did not provide notable benefits over diquafosol monotherapy, but the dual treatment might help reduce adverse events compared with diquafosol alone. Rebamipide seemed to improve corneal fluorescein staining and TBUT compared with artificial tears, but these were not statistically significant. Eledoisin was ranked the best in the network of ST, but it could significantly worsen TBUT. MIM-D3 seemed to worsen OSDI scores. RhNGF significantly increased corneal fluorescein staining compared with artificial tears, diquafosol, and rebamipide.

A network of ST showed incongruous results compared with other outcome networks. Only eledoisin and PRP significantly improved Schirmer scores compared with artificial tears. This finding could be explained by a high sensitivity of ST, which is linked to poorly controllable factors, such as the position of a Schirmer strip, reflex tearing from eye irritation, tear evaporation, temperature, and humidity.[38] ST results should be carefully interpreted along with other outcome parameters.

Our findings support the TFOS DEWS 2017 treatment guidelines for DED,[7] which recommend a sequence of treatments, beginning with conventional and commonly available therapies such as artificial tears for early-stage disease, then step up to more advanced therapies such as topical secretagogues and serum eye drops in patients who are failed by the previous steps. We further added the ranking information for each treatment category for each dry eye outcome. It should be noted that CSA is not an interesting intervention in our study because of its distinct mechanism of anti-inflammation by blocking T-cell activity. Only 3 RCTs[e37–e39] comparing between CSA and topical secretagogues were eligible for our study.

This study has some limitations. First, most of the eligible RCTs were judged to be at high risk of bias, which led to downgrading the certainty of overall network results. Future high-quality RCTs comparing several interventions are warranted to confirm our findings. Second, there was a wide range of measurement methods used for evaluating dry eye symptom and ocular surface staining. Only RCTs reporting OSDI scores and corneal fluorescein staining were included in our analyses. In addition, other dry eye parameters such as tear osmolarity and tear meniscus height could not be evaluated because of insufficient information. Third, although subgroup analysis was performed in the direct meta-analysis, this analysis was not applicable for the NMA because of insufficient baseline data across the included studies in the network and sparse number of studies in each treatment comparison. Finally, we considered only short-term treatment outcomes (2–12 weeks). Long-term efficacy and safety of these interventions could not be established.

CONCLUSIONS

Based on our evidence, biological tear substitutes, including AS, CBS, APL, and PRP, might be the most effective treatment among tear promotion eye drops in relieving dry eye symptoms without increasing adverse events. Among topical secretagogues, only diquafosol showed obvious beneficial effects on improving dry eye symptoms over artificial tears. However, there was an evidence uncertainty because of sparse data and low quality of the primary studies. A clinical decision regarding the use of any kind of tear promotion eye drops should be considered along with patient preferences, cost-effectiveness, and treatment availability.

ACKNOWLEDGMENTS

This manuscript is a part of P. Jongkhajornpong's training in an international PhD program (Clinical Epidemiology) at the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, and this study formed part of her dissertation.

REFERENCES

1. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II epidemiology report. *Ocul Surf*. 2017;15:334–365.
2. Sullivan DA, Rocha EM, Aragona P, et al. TFOS DEWS II sex, gender, and hormones report. *Ocul Surf*. 2017;15:284–333.
3. McDonald M, Patel DA, Keith MS, et al. Economic and humanistic burden of dry eye disease in Europe, North America, and Asia: a systematic literature review. *Ocul Surf*. 2016;14:144–167.
4. Mizuno Y, Yamada M, Miyake Y. Association between clinical diagnostic tests and health-related quality of life surveys in patients with dry eye syndrome. *Jpn J Ophthalmol*. 2010;54:259–265.
5. Miljanović B, Dana R, Sullivan DA, et al. Impact of dry eye syndrome on vision-related quality of life. *Am J Ophthalmol*. 2007;143:409–415.
6. Yu J, Asche CV, Fairchild CJ. The economic burden of dry eye disease in the United States: a decision tree analysis. *Cornea*. 2011;30:379–387.
7. Jones L, Downie LE, Korb D, et al. TFOS DEWS II management and therapy report. *Ocul Surf*. 2017;15:575–628.
8. Wu D, Chen WQ, Li R, et al. Efficacy and safety of topical diquafosol ophthalmic solution for treatment of dry eye: a systematic review of randomized clinical trials. *Cornea*. 2015;34:644–650.
9. Nam K, Kim HJ, Yoo A. Efficacy and safety of topical 3% diquafosol ophthalmic solution for the treatment of multifactorial dry eye disease: meta-analysis of randomized clinical trials. *Ophthalmic Res*. 2019;61:188–198.
10. Pan Q, Angelina A, Marrone M, et al. Autologous serum eye drops for dry eye. *Cochrane Database Syst Rev*. 2017;2:CD009327.
11. Pan Q, Angelina A, Zambrano A, et al. Autologous serum eye drops for dry eye. *Cochrane Database Syst Rev*. 2013;8:CD009327.
12. Franchini M, Cruciani M, Mengoli C, et al. Serum eye drops for the treatment of ocular surface diseases: a systematic review and meta-analysis. *Blood Transfus*. 2019;17:200–209.
13. Azari AA, Rapuano CJ. Autologous serum eye drops for the treatment of ocular surface disease. *Eye Contact Lens*. 2015;41:133–140.
14. Zhao X, Xia S, Chen Y. Comparison of the efficacy between topical diquafosol and artificial tears in the treatment of dry eye following cataract surgery: a meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2017;96:e8174.
15. Holland EJ, Darvish M, Nichols KK, et al. Efficacy of topical ophthalmic drugs in the treatment of dry eye disease: a systematic literature review. *Ocul Surf*. 2019;17:412–423.

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16. Rohatgi A. WebPlotDigitizer. 2019. Available at: https://automeris.io/WebPlotDigitizer/ed. Accessed January 15, 2020.
17. Yang YJ, Lee WY, Kim YJ, et al. A meta-analysis of the efficacy of hyaluronic acid eye drops for the treatment of dry eye syndrome. *Int J Environ Res Public Health*. 2021;18:2383.
18. Ribeiro M, Barbosa FT, Ribeiro LEF, et al. Effectiveness of using preservative-free artificial tears versus preserved lubricants for the treatment of dry eyes: a systematic review. *Arq Bras Oftalmol*. 2019; 82:436–445.
19. Ang BCH, Sng JJ, Wang PXH, et al. Sodium hyaluronate in the treatment of dry eye syndrome: a systematic review and meta-analysis. *Sci Rep*. 2017;7:9013.
20. Song JK, Lee K, Park HY, et al. Efficacy of carboxymethylcellulose and hyaluronate in dry eye disease: a systematic review and meta-analysis. *Korean J Fam Med*. 2017;38:2–7.
21. Kong X, Yan C, Ma W, et al. Sodium hyaluronate's effect on xerophthalmia: a meta-analysis of randomized controlled trials. *Curr Med Res Opin*. 2016;32:477–484.
22. Pucker AD, Ng SM, Nichols JJ. Over the counter (OTC) artificial tear drops for dry eye syndrome. *Cochrane Database Syst Rev*. 2016;2: CD009729.
23. Doughty MJ, Glavin S. Efficacy of different dry eye treatments with artificial tears or ocular lubricants: a systematic review. *Ophthalmic Physiol Opt*. 2009;29:573–583.
24. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
25. Elbourne DR, Altman DG, Higgins JPT, et al. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol*. 2002;31: 140–149.
26. Wolffsohn JS, Arita R, Chalmers R, et al. TFOS DEWS II diagnostic methodology report. *Ocul Surf*. 2017;15:539–574.
27. Chaimani A, Higgins JPT, Mavridis D, et al. Graphical tools for network meta-analysis in STATA. *PLoS One*. 2013;8:e76654.
28. Brignardello-Petersen R, Bonner A, Alexander PE, et al. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. *J Clin Epidemiol*. 2018;93:36–44.
29. Brignardello-Petersen R, Murad MH, Walter SD, et al. GRADE approach to rate the certainty from a network meta-analysis: avoiding spurious judgments of imprecision in sparse networks. *J Clin Epidemiol*. 2019;105:60–67.
30. Puhan MA, Schünemann HJ, Murad MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ*. 2014;349:g5630.
31. Salanti G, Del Giovane C, Chaimani A, et al. Evaluating the quality of evidence from a network meta-analysis. *PLoS One*. 2014;9:e99682.
32. Brignardello-Petersen R, Mustafa RA, Siemieniuk RAC, et al. GRADE approach to rate the certainty from a network meta-analysis: addressing incoherence. *J Clin Epidemiol*. 2019;108:77–85.
33. Miller KL, Walt JG, Mink DR, et al. Minimal clinically important difference for the ocular surface disease index. *Arch Ophthalmol*. 2010; 128:94–101.
34. Drew VJ, Tseng CL, Seghatchian J, et al. Reflections on dry eye syndrome treatment: therapeutic role of blood products. *Front Med (Lausanne)*. 2018;5:33.
35. Kim KM, Shin YT, Kim HK. Effect of autologous platelet-rich plasma on persistent corneal epithelial defect after infectious keratitis. *Jpn J Ophthalmol*. 2012;56:544–550.
36. Villatoro AJ, Fernández V, Claros S, et al. Regenerative therapies in dry eye disease: from growth factors to cell therapy. *Int J Mol Sci*. 2017;18: 2264.
37. Yoon KC, Im SK, Park YG, et al. Application of umbilical cord serum eyedrops for the treatment of dry eye syndrome. *Cornea*. 2006;25: 268–272.
38. Kallarackal GU, Ansari EA, Amos N, et al. A comparative study to assess the clinical use of fluorescein meniscus time (FMT) with tear break up time (TBUT) and Schirmer's tests (ST) in the diagnosis of dry eyes. *Eye (Lond)*. 2002;16:594–600.

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