REVIEW ARTICLE

Efficacy, safety, and tolerability of pharmacological treatments for moderate-to-severe dry eye disease: a systematic review

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Abstract

Dry eye disease is characterized by impaired tear film homeostasis and ocular surface inflammation. Topical ocular medications for moderate-to-severe dry eye disease include hyaluronic acid (HA), cyclosporine A (CsA), serum eyedrops, and lifitegrast. Effective HA-based formulations and regimens include topical aqueous HA 0.15% and 0.18%, HA gel 0.30%, sequential administration of HA 0.30% and 0.15%, a combination of HA 0.15% and polyethylene glycol, and multi-agent eyedrops containing 0.15% HA. Preservative-free hydrocortisone and loteprednol, known as soft steroids, are effective and have a reduced risk of steroid-related adverse effects. Effective CsA formulations include 0.05% CsA gel, CsA nanoemulsions, water-free CsA, and CsA combinations with lubricants (eg, HA). Autologous, allogeneic, and umbilical cord serum eyedrops, as well as the novel lymphocyte function-associated antigen-1 antagonist lifitegrast, are also effective. Various treatment options may improve treatment adherence. Long-term and large-scale studies are required to confirm the therapeutic efficacies of these treatments.

Key words: *Cyclosporine; Dry eye syndromes; Hyaluronic acid; Lifitegrast; Ophthalmic solutions*

Introduction

Dry eye disease (DED) is characterized by tear film instability and ocular surface inflammation, resulting in ocular distress and visual impairment.[1] Despite its increasing incidence worldwide, DED is commonly underdiagnosed.[2-4] Moderate-to-severe DED can result in substantial decreases in productivity and daily activities.[5] Currently, treatments for DED are not standardized.[6,7] In this systematic review, we aimed to analyze the effectiveness and safety of five therapeutic options for moderate-to-severe DED: hyaluronic acid (HA), topical steroids, cyclosporine A (CsA), serum eyedrops, and lifitegrast. Additionally, we sought to provide guidance concerning selection of appropriate treatment options for moderate-to-severe DED. Other treatment options (eg, topical and oral secretagogues, tacrolimus, macrolides, and vitamins A and E) were not included in the analysis owing to the unavailability of secretagogues in

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Hong Kong, the specific use of tacrolimus for lid eczema, the targeted nature of macrolides for meibomian gland dysfunction, and the roles of vitamin A and E as additives in lubricants and ointments, respectively.

Methods

On 30 December 2023, we searched PubMed using the keywords 'moderate to severe dry eye disease' AND 'treatment'. We identified 450 randomized controlled studies written in English and published between 2015 and 2023. After excluding duplicates, reviews, editorials, and case reports/series, as well as studies of other treatment options, we included 20 studies related to the five treatment options (HA, topical steroids, CsA, serum eyedrops, and lifitegrast) for moderate-to-severe DED, which was defined as a severity level of ≥2 according to the Dry Eye Workshop I grading scheme.[8]

Hyaluronic acid

HA is a viscoelastic anionic glycosaminoglycan that binds water and resists dehydration, thereby increasing ocular surface lubrication, tear stability, epithelium healing, and relief of DED symptoms.[9,10] Although topical HA at concentrations of 0.1% to 0.2% is effective for milder DEDs,[11-13] its therapeutic efficacy for moderate-to-severe DED remains unclear.

Topical HA at concentrations of 0.15% to 0.30% was effective for moderate-to-severe DED (**Table 1**). Topical 0.15% HA was comparable to 0.05% CsA in terms of improving tear breakup time (TBUT), corneal staining score (CSS1), strip meniscometry score, and ocular surface disease index (OSDI) after 12 weeks (all $p<0.05$).[14] In addition, topical 0.18% HA drops were effective in improving the CSS1, conjunctival staining score, TBUT,

Table 1. Studies of hyaluronic acid for moderate-to-severe dry eye disease

Study	No. of patients	Intervention	Evaluation timepoint	Findings	Limitations
Lee et al,[14] 2022	438	0.15% HA drop 6 times daily vs 0.05% CsA drop twice + 0.5% carboxymethylcellulose medication 6 times daily vs 0.15% HA 6 times + 0.05% CsA twice daily	Baseline, weeks 4 and 12	0.05% CsA and 0.15% HA were comparable in terms of improvements in CSS1, TBUT, SMS, and OSDI. 0.15% HA was well-tolerated and had lower prevalence of TRAEs.	Different instillation frequencies among groups, short follow-up period, concomitant effect from co-existing carboxymethylcellulose medication
Calonge et al,[15] 2023	70	0.30% HA gel vs 0.18% HA drop 4 to 6 times daily	Baseline, days 35 and 84	0.18% HA improved CSS1, CSS2, TBUT, DEQ-5, and ODSS at 84 days (all $p<0.001$). Both 0.18% HA drop and 0.30% HA gel were comparable in terms of CSS1, CSS2, TBUT, DEQ-5, and ODSS. Both HA formulations were well-tolerated, and no serious TRAEs were reported.	Short follow-up, small sample size, lack of placebo group, different etiologies causing biased results
Jun et al,[16] 2022	76	0.30% HA drop (1 drop) followed by 0.15% HA drop (1 drop) vs 0.30% HA drop (2 drops) vs 0.15% HA drop (2 drops) 4 times daily	Baseline, weeks 4 and 8	Compared with 0.15% and 0.30% HA monotherapies, HA combination therapy is superior in terms of CSS1 ($p<0.001$) and OSDI ($p=0.037$). All formulations were well-tolerated, and no serious TRAEs were reported.	Short follow-up, lack of placebo group, open-label design (participants not blinded)
Labetoulle et al,[17] 2022	78	Polyethylene glycol solution (0.15% HA and 0.5% PEG 8000) vs sodium hyaluronate (0.18% HA) 3 to 6 times daily as needed	Baseline, days 28 and 90	Compared with 0.18% HA monotherapy, polyethylene glycol solution showed greater improvements in OSD-QoL, CSS1, and TBUT at 90 days (all $p<0.05$). Both drops were well-tolerated; no serious TRAEs were reported.	Short follow-up
Roszkowska et al,[18] 2022	4	CXHAL drops vs trehalose drops 4 times daily	Baseline, day 60	At 2 months, CXHAL drops showed significant improvements in SANDE ($p=0.001$), TBUT ($p<0.001$), and staining ($p=0.004$). Both CXHAL and trehalose were generally safe and well-tolerated; no serious TRAEs were reported.	Small sample size, short follow-up

Abbreviations: CsA=cyclosporine A, CSS1=corneal staining score, CSS2=conjunctival staining score, CXHAL=cross-linked hyaluronic acid, trehalose, liposomes, and stearylamine, DEQ-5=5-item Dry Eye Questionnaire, HA=hyaluronic acid, ODSS=ocular dryness symptoms score, OSDI=ocular surface disease index, OSD-QoL=Ocular Surface Disease-Quality of Life, PEG=poly(ethylene glycol), SANDE=Symptom Assessment iN Dry Eye, SMS=strip meniscometry score, TBUT=tear breakup time, TRAE=treatment-related adverse event.

ocular dryness symptoms score, and 5-Item-Dry-Eye-Questionnaire score after 12 weeks (all p<0.001).[15] Both 0.30% HA gel and 0.18% HA aqueous drops improved the CSS1, TBUT, ocular dryness symptoms score, and 5-Item-Dry-Eye-Questionnaire score after 12 weeks (all p<0.001); no dose-response relationship was observed.[15]

A single 0.30% HA drop followed by a single 0.15% HA drop significantly improved signs and symptoms (all p<0.05) and outperformed monotherapy with either HA drop in terms of the CSS1 (p<0.001) and OSDI (p=0.037) at 8 weeks.[16] The effectiveness of HA was not dose-dependent; the combination of 0.30% and 0.15% HA drops outperformed monotherapy with 0.30% HA drop. Compared with 0.18% HA monotherapy, a combination of 0.15% HA and polyethylene glycol resulted in greater improvements in CSS1, TBUT, and Ocular Surface Disease-Quality of Life questionnaire scores at 12 weeks (all p<0.05).[17] CXHAL drops (containing 0.15% cross-linked HA, 3% trehalose, 1% liposomes, and 0.25% stearylamine) significantly improved TBUT (p<0.001), corneoconjunctival staining (p=0.004), and Symptom Assessment in Dry Eye score (p=0.001) at 8 weeks.[18]

Concerning safety and tolerability, 0.15% aqueous HA, 0.18% aqueous HA, 0.30% HA gel, the 0.15% HA and 0.30% HA combination, polyethylene glycol, and CXHAL are well-tolerated and generally safe to use. Most treatment-related adverse events (TRAEs) have been mild to moderate; patients were satisfied with the various HA regimens, formulations, and combinations.

Topical aqueous HA at concentrations of 0.15% and 0.18% is likely to provide effective relief for moderate-to-severe DED. Aqueous HA drops at concentrations of >0.18% have better ocular surface healing effects[11,19,20] but are associated with suboptimal treatment outcomes (eg, hazy vision and ocular discomfort).[19,21,22] HA gels enable administration of higher HA concentrations in a form that patients can tolerate. However, considering the non-dose-dependent relationship, it is unclear whether a higher HA concentration will have a greater therapeutic benefit. HA gels enable longer HA retention when administered before bedtime. Alternatively, combinations of HA with different lubricants can enhance the effects of HA; all-in-one HA drops can increase HA effectiveness while improving patient convenience and satisfaction.

Topical steroids

Topical steroids exert anti-inflammatory effects by reducing cytokine expression, preserving corneal epithelium integrity, enhancing tear production, and decreasing pro-inflammatory cytokine levels in tears.[23-25] However, conventional steroid drops (eg, methylprednisolone and fluorometholone) often have adverse effects such as elevated intraocular pressure (IOP) and cataract development.[26] Newer steroid formulations, known as soft steroids, such as preservative-free hydrocortisone (PFH) and loteprednol can minimize adverse effects while maintaining anti-inflammatory efficacy by limiting penetration through the anterior chamber.[27-29] These newer drugs have reduced risks of elevated IOP and cataract development.

Regarding efficacy, in patients with Sjogren syndrome, a short-term pulsed regimen of topical 0.335% (low-dose) PFH over 3 consecutive months, followed by alternating discontinuation and resumption of treatment in a 1-month interval for 3 months, effectively improved corneoconjunctival staining, tear film osmolarity, and OSDI (all p<0.05) [**Table 2**].[30] Pulsed PFH demonstrated rapid symptom improvement and sustained anti-inflammatory

Table 2. Studies of hyaluronic acid for moderate-to-severe dry eye disease

Studies	No. of patients	Intervention	Evaluation timepoint	Findings	Limitations
Menchini et al,[30] 2023	40 with Sjogren syndrome	Topical PFH for 6 days with a pulsed posology: 3 times daily for 2 days, twice daily for 2 days, and once daily for 2 days for 3 consecutive months, followed by alternating discontinuation and resumption of treatment in a 1-month interval for 3 months	Baseline, months 3 and 6	Topical PFH regimen improved OSDI, CSS1, CSS2, and tear film osmolarity throughout the study period (all p<0.05). There was no significant change in IOP at any timepoint.	Retrospective study design, short follow-up, non-uniform concomitant topical lubricant treatments, lack of control group
Yin et al,[31] 2018	42, including 21 with chronic graft-vs-host-disease	Loteprednol etabonate 0.5% vs artificial tears twice daily	Baseline, week 4	In patients without graft-vs-host disease, loteprednol treatment decreased the mean OSDI score by 34% (p=0.001) and the mean corneal fluorescein staining score by 41% (p=0.02). In patients with graft-vs-host disease, loteprednol treatment led to minimal changes in OSDI (p=0.85) and corneal fluorescein staining (p=0.1).	Small sample size, lack of exclusion criteria concerning pre-existing ophthalmic regimens

Abbreviations: CSS1=corneal staining score, CSS2=conjunctival staining score, IOP=intraocular pressure, OSDI=ocular surface disease index, PFH=preservative-free hydrocortisone.

effects beyond the treatment period; there were no significant differences in OSDI and TBUT values at 3 and 6 months. In patients without graft-vs-host disease, twice-daily application of loteprednol etabonate 0.5% (low-dose) ophthalmic suspension for 4 weeks significantly reduced OSDI (p=0.01) and corneal fluorescein staining (p=0.02).[31] However, patients with graft-vs-host disease experienced minimal changes in OSDI (p=0.1) and corneal fluorescein staining (p=0.85).[31]

Concerning safety, both PFH with pulsed posology and loteprednol etabonate 0.5% drops are generally safe. The topical PFH regimen showed a high level of safety, with no significant changes in IOP.[30] Loteprednol etabonate 0.5% drops had low rates of TRAEs and minimal impact on IOP.[32,33] There were no specific safety concerns associated with the use of loteprednol etabonate 0.5% drops.[31]

PFH drops exhibit efficacy and safety comparable to conventional topical steroid drops (methylprednisolone and fluorometholone) for moderate-to-severe DED, particularly among patients with Sjogren syndrome.[30] Additionally, short-term (4 weeks) use of topical 0.5% (low-dose) loteprednol etabonate was effective in patients without graft-vs-host disease.[31] PFH drops used in a pulsed regimen demonstrated prolonged efficacy despite treatment cessation.[30] Soft steroids with a pulsed and tapered dosing schedule (6 days/month) can be used in patients with moderate-to-severe DED, especially those with Sjogren syndrome for whom lubricants alone are insufficient.[30] Further research is needed to confirm the role of soft steroids as a transitional therapy before CsA eye drops take full effect. However, in patients with graft-vs-host disease, topical steroids may have reduced efficacy and necessitate more frequent or prolonged treatment.[31] Stronger anti-inflammatory medications, such as CsA and lifitegrast, may be used to manage ocular surface inflammation in these patients.[31]

Cyclosporine A

Topical CsA suppresses inflammatory activities such as interleukin-2-mediated T-cell activation and lymphocyte migration.[34] Although topical 0.05% CsA is effective for moderate-to-severe DED,[35] its aqueous formulation is associated with ocular burning and stinging,[36-38] which reduces patient adherence[39,40] and leads to lower therapeutic effectiveness.[38,41,42]

Novel gel and nanoemulsion formulations of CsA can significantly improve the signs and symptoms of moderate-to-severe DED (**Table 3**).[43-46] Compared with 0.05% aqueous CsA, all 0.05% CsA gel (CyclAGel) regimens (0.05% once daily, 0.05% twice daily, and 0.1% once daily) improved the CSS1, TBUT, and Schirmer test score (ST1) at 12 weeks (all p<0.05).[43] Furthermore, CyclAGels have greater overall effects than aqueous CsA; the once-daily regimen of 0.05% CyclAGel provided the greatest efficacy. In a phase III trial, the once-daily regimen of 0.05% CyclAGel elicited positive clinical response; a higher proportion of patients experienced at least a 1-point improvement in the inferior CSS1 (p<0.0001) and a greater improvement in the ST1 (p<0.05) by day 84, compared with the vehicle.[44] Similarly, a 0.08% CsA nanoemulsion preparation (TJO-087) significantly improved the OSDI, TBUT, CSS1, and ST1 at 32 weeks.[45] A 0.05% CsA micellar nanoparticle preparation yielded superior improvements in the CSS1, ST1, OSDI, and individual dry eye symptom scores, compared with an equivalent dose of aqueous CsA (p<0.05).[46]

In the ESSENCE-2 trial, water-free CsA (0.1%) demonstrated early therapeutic effects on the ocular surface, along with greater improvements in the total corneal fluorescein score at 15 days (p<0.05) and 29 days (p=0.03) and the central corneal fluorescein score at 15 days (p<0.05), compared with the aqueous vehicle.[47] Combinations of lower-concentration CsA with trehalose (0.01% CsA and 3% trehalose; 0.02% CsA and 3% trehalose) resulted in significant improvements in the CSS1, conjunctival staining score, TBUT, and Standard Patient Evaluation of Eye Dryness Questionnaire score (all p<0.05) at 12 weeks.[48] A combination of CsA with HA significantly reduced tear interleukin-6 levels at 1 month, compared with 0.1% CsA monotherapy (p<0.05).[49] The percentages of improvement in the OSDI, TBUT, and ocular staining were consistently greater in the combination treatment group.

All CsA gel regimens and nanoparticle formulations are safe and well-tolerated, as are water-free CsA. No serious TRAEs have been recorded. Two major adverse events were reported in the water-free CsA trial, but they were not linked to the study drug. Patients receiving CsA combination therapies reported high levels of treatment satisfaction and no TRAEs.

Novel CsA formulations and combinations may enhance the effectiveness of topical CsA. Gels and nanoemulsions may improve treatment satisfaction and drug adherence, whereas the water-free formulation enables more rapid onset of therapeutic effects, thereby increasing treatment adherence despite modest TRAEs. The reduced tear interleukin-6 levels suggest that combination therapies can enhance the anti-inflammatory effects of CsA.

Serum eyedrops

Blood derivatives supply tear components (eg, growth factors, vitamins, and proteins) to the ocular surface.[50] Blood sources are from the patient's own peripheral blood (autologous) and donor tissues, particularly allogeneic peripheral blood and umbilical cord blood.[51] These serum eyedrops are intended for patients with severe DEDs who have not responded to HA or CsA.[52]

Autologous serum eyedrops (ASEs), allogeneic serum eyedrops (HSEs), and umbilical cord serum eyedrops (USEs) are effective treatments for moderate-to-severe DED. Both 20% and 50% ASE preparations improved

Table 3. Studies of cyclosporine A for moderate-to-severe dry eye disease

Studies	No. of patients	Intervention	Evaluation timepoint	Significant findings	Limitations
Peng et al,[43] 2021	240	0.05% CyclAGel once daily vs 0.05% CyclAGel twice daily vs 0.1% CyclAGel once daily vs 0.05% Restasis twice daily	Baseline, weeks 2, 6, and 12	Compared with 0.05% aqueous CsA, all 0.05% CyclAGel regimens improved the eye dryness score, dryness symptoms, CSS1, TBUT, and ST1 at 12 weeks (all p<0.05). 0.05% CyclAGel once daily showed the greatest overall efficacy. No serious TRAEs were noted; all CyclAGel regimens were safe and well-tolerated.	Open-label design, biased perception of symptom reporting due to formulation differences
Peng et al,[44] 2022	627	0.05% CyclAGel vs vehicle drops once nightly	Baseline, days 14, 42, and 84	Compared with patients receiving vehicle drops, more patients receiving 0.05% CyclAGel once nightly experienced at least a 1-point improvement in inferior CSS1 (p<0.0001) and a greater improvement in ST1 (p<0.05) by day 84. 0.05% CyclAGel once nightly was well-tolerated, and no serious TRAEs were reported.	Short follow-up, limited inclusion of patients with different DED etiologies
Eom et al,[45] 2023	155	0.08% nanoemulsion CsA (TJO-087) once daily vs 0.05% emulsion CsA twice daily	Baseline, weeks 8, 16, 24, and 32	TJO-087 and CsA 0.05% showed similar improvements in OSDI, TBUT, CSS1, and ST1 at 32 weeks. TJO-087 was well-tolerated, and no serious TRAEs were reported.	Possible unblinding of blinded design, confounding effect from concomitant carboxymethylcellulose medication
Rao et al,[46] 2023	90	0.05% CsA MNP twice daily for the entire period vs 0.05% CsA MNP twice daily for the first 4 weeks and once daily for the remaining period vs 0.05% Restasis twice daily for the entire period	Baseline, weeks 4, 8, 12, and 24	Compared with Restasis, both CsA MNP formulations yielded superior improvements in CSS1, ST1, OSDI, and individual dry eye symptom scores (all p<0.05). No serious TRAEs were reported, and both MNP formulations were well-tolerated.	Endpoints susceptible to bias (eg, symptom score), short follow-up
Akpek et al,[47] 2023	817	Water-free 0.1% CsA drops vs vehicle twice daily	Baseline, days 15 and 29	Water-free CsA yielded superior improvements in total corneal fluorescein score at 15 days (p<0.05) and 29 days (p=0.03) and in central corneal fluorescein score at 15 days (p<0.05). Two serious TRAEs were documented; neither was associated with the study drug.	Inclusion of mainly aqueous-deficient DED patients, short follow-up
Shin et al,[48] 2021	114	HU00701 (0.01% CsA + 3% trehalose) vs HU007 (0.02% CsA + 3% trehalose) vs placebo vs 0.05% Restasis (0.05% CsA)	Baseline, weeks 4, 8, and 12	Both HU00701 and HU007 significantly improved CSS1, CSS2, TBUT, and SPEED score by week 12 (all p<0.05). Both resulted in no major TRAEs and were well-tolerated.	Unclear minimum therapeutic dose of CsA, unclear synergistic effects between CsA and trehalose, phase II study without active competitor, Restasis only served as reference treatment
Priani et al,[49] 2023	20	0.1% CsA vs 0.1% CsA + 0.1% HA 1 drop once daily	Baseline, month 1	Compared with patients receiving CsA 0.1% monotherapy, more patients receiving combination therapy experienced improvements in OSDI, TBUT, ocular staining, and interleukin-6 levels. The CsA/HA combination was generally safe and well-tolerated.	Small sample size, short follow-up period

Abbreviations: CsA=cyclosporine A, CyclAGel=cyclosporine A gel, CSS1=corneal staining score, CSS2=conjunctival staining score, DED=dry eye disease, HA=hyaluronic acid, MNP=micellar nanoparticle, OSDI=ocular surface disease index, SPEED=Standard Patient Evaluation of Eye Dryness, ST1=Schirmer test score, TBUT=tear breakup time, TRAE=treatment-related adverse event.

the subjective and objective parameters of moderate DED (all p<0.05) [**Table 4**].[53] However, only the 50% ASE preparation was effective in improving subjective and objective parameters of severe DED at 12 weeks (all p<0.05). HSEs and ASEs demonstrated similar efficacy in terms of improving the OSDI, TBUT, punctate lesions, and visual acuity by 1 month.[54] USEs and ASEs produced persistent improvements in TBUT and tear protein levels (eg, lysozyme) at 12 weeks.[55] All three types of serum eyedrops were similarly effective in terms of improving TBUT, ST1, visual acuity, and the fluorescein staining score among patients with severe DED.[56]

All three serum eyedrops are generally well-tolerated and safe to use. Only one study reported mild transient TRAEs after the use of ASEs and HSEs.

Table 4. Studies of serum eyedrops for moderate-to-severe dry eye disease

Studies	No. of patients	Intervention	Evaluation timepoint	Findings	Limitations
Kumari et al,[53] 2023	44	20% ASE vs 50% ASE	Baseline, weeks 2, 4, 8, and 12	In moderate DED, both 20% and 50% ASE improved subjective and objective parameters ($p<0.05$), but in severe DED, only 50% ASE improved both objective and subjective parameters ($p<0.05$). Both ASE preparations were generally safe and well-tolerated. No serious TRAEs were documented.	Need for refrigeration during storage, short follow-up, lack of lissamine green and rose bengal staining, lack of impression cytology for ocular surface
van der Meer et al,[54] 2021	19	ASEs vs HSEs	Baseline, month 1	ASEs and HSEs were comparable in terms of OSDI, TBUT, tear production, punctate lesions, and visual acuity. Both were well-tolerated and safe for use. TRAEs were mild and resolved completely.	Lack of inclusion criteria regarding graft-vs-host disease or Stevens-Johnson syndrome, small sample size
Mukhopadhyay et al,[55] 2015	144 with Hansen's disease	ASEs vs USEs	Baseline, weeks 6 and 12	Both USEs and ASEs significantly improved TBUT and tear protein levels at 12 weeks. Both were well-tolerated, and no serious TRAEs were reported.	Short follow-up, possible confounding effects from systemic antileprosy therapy
Rodríguez Calvo-de-Mora et al,[56] 2022	63 (21 per arm)	ASEs vs HSEs vs USEs	Baseline, months 1 and 3	All 3 therapies had similar effects in terms of improving visual acuity, ST1, TBUT, fluorescein and lissamine green staining scores, and questionnaire scores. All 3 therapies had good tolerability and safety. No TRAEs were documented.	Limited number of molecules determined and analyzed, lack of conjunctival impression cytology, lack of control group receiving conventional treatment

Abbreviations: ASE=autologous serum eyedrop, DED=dry eye disease, HSE=allogeneic serum eyedrop, OSDI=ocular surface disease index, ST1=Schirmer test score, TBUT=tear breakup time, TRAE=treatment-related adverse event, USE=umbilical cord serum eyedrop.

The 20% ASE preparation is effective for moderate DED, whereas the 50% ASE preparation is effective for severe DED. HSEs and USEs are effective for moderate-to-severe DED in patients who are unable to provide blood owing to logistical or clinical restrictions.

Lifitegrast

Lifitegrast is a lymphocyte function-associated antigen-1 antagonist specifically designed to treat DED.[57] By suppressing T-cell adherence to intercellular adhesion molecule 1, lifitegrast prevents the interaction of integrin lymphocyte function-associated antigen-1 and intercellular adhesion molecule 1, thereby inhibiting the inflammatory cascade associated with DED.[58,59] Lifitegrast is used in the treatment of patients with severe DED who exhibit resistance to standard DED medications such as HA and CsA.[60]

Two phase III trials evaluated the efficacy of lifitegrast in patients with moderate-to-severe DED (ie, a corneal fluorescein staining score of >1.5 and an eye dryness score of ≥60) [**Table 5**].[61,62] In the OPUS-2 trial, compared with placebo, lifitegrast treatment did not lead to greater improvements in the inferior corneal fluorescein staining score ($p=0.6186$), total CSS1 ($p=0.3711$), or nasal lissamine staining score ($p=0.6982$) at 84 days; however, it significantly improved the eye dryness score ($p<0.0001$), ocular discomfort score ($p=0.001$), and eye discomfort score ($p<0.0001$) at 84 days.[61] In the OPUS-3 study, lifitegrast was superior to placebo in improving the eye dryness score, symptoms of itching ($p=0.032$), foreign body sensations ($p=0.042$), and eye discomfort ($p=0.005$) at 42 days, although lifitegrast did not exhibit greater effectiveness by day 84.[62] Post hoc analysis further demonstrated the efficacy of lifitegrast against moderate-to-severe DED at all endpoints ($p\leq0.001$).[63] The greatest improvement was observed in patients with an inferior corneal fluorescein staining score of >1.5 and an eye dryness score of ≥60 at baseline.

Lifitegrast appears to be well-tolerated and safe. There have been no reports of serious ocular TRAEs; all TRAEs have been mild to moderate.

Lifitegrast is superior to topical CsA among patients with moderate-to-severe DED. Lifitegrast is effective as early as day 14. In contrast, topical CsA tends to have a delayed onset, and 16% to 29% of patients who use topical CsA may experience pain/irritation/burning in the eye.[64,65]

Discussion

The optimal approach for management of moderate-to-severe DED is a stepwise and sequential approach. In patients with moderate-to-severe DED, HA drops can be used as the primary daytime treatment. Instillations of topical 0.15% HA drops six times daily for 12 weeks provides relief comparable to CsA. For nighttime therapy requiring longer retention, a 0.30% HA gel formulation is recommended. It is important to note that the effectiveness of HA is not dose-dependent. Therefore, increased concentrations may not provide greater benefits. Combination HA therapies involving different lubricants can enhance the efficacy of HA, but further research is needed to confirm this finding.

Table 5. Studies of lifitegrast for moderate-to-severe dry eye disease

Studies	No. of patients	Intervention	Evaluation timepoint	Findings	Limitations
Tauber et al,[61] 2015	718, including 413 with moderate-to-severe DED	Lifitegrast vs placebo twice daily	Baseline, days 14, 42, and 84	Compared with placebo, lifitegrast yielded superior improvements in eye dryness (p<0.0001), ocular discomfort (p=0.0005), and eye discomfort (p<0.0001). Lifitegrast was generally well-tolerated and safe. Most TRAEs were mild to moderate.	Short follow-up, selection bias (inclusion of patients actively using artificial tears), exclusion of patients with active lid margin disease
Holland et al,[62] 2017	711, including 390 with moderate-to-severe DED	Lifitegrast vs placebo twice daily	Baseline, days 14, 42, and 84	Lifitegrast yielded superior improvements in symptoms of itching (p=0.032), foreign body sensations (p=0.042), and eye discomfort (p=0.005) at 42 days. Lifitegrast was generally safe and well-tolerated. Most TRAEs were mild to moderate.	Short follow-up, exclusion of patients with a history of LASIK in preceding 12 months and patients wearing contact lenses

Abbreviations: DED=dry eye disease, LASIK=laser in situ keratomileusis, TRAE=treatment-related adverse event.

For patients who do not respond to the HA regimen, short-term use of topical soft steroids (eg, a pulsed regimen of PFH and loteprednol) is recommended. Topical soft steroids display efficacy comparable to conventional steroid drops while providing superior safety benefits with minimal effects on IOP. Short-term pulsed topical PFH is particularly beneficial for patients with Sjogren syndrome. However, topical soft steroids may be less effective in patients with graft-vs-host disease; these patients may require more frequent or longer duration of treatment.[31] Alternatively, immunomodulatory agents such as CsA and lifitegrast can be used for ocular surface inflammation in patients with graft-vs-host disease.[31] These medications have stronger anti-inflammatory effects and may be useful for patients who do not adequately respond to soft steroids.[31] The use of 5.0% lifitegrast or 0.05% CsA twice daily for at least 12 weeks can alleviate symptoms of moderate-to-severe DED.[38,62,66] Patients with intolerable adverse effects from topical aqueous CsA can switch to gel or nanoemulsion formulations of CsA. Effective regimens include 0.05% CyclAGel once daily for 12 weeks and 0.08% nanoemulsion CsA (TJO-087) once daily for 32 weeks. Lifitegrast is recommended for patients who are sensitive to the adverse effects of aqueous CsA.

Patients who do not respond to anti-inflammatory medications, such as steroids and immunomodulatory agents, may consider ASEs. For moderate DED, we recommend using a 20% ASE preparation four times daily for 2 to 4 weeks. The 20% concentration is intended to prevent excessive antiproliferative effects.[67] However, a 50% ASE preparation may be needed for patients with severe DED. ASEs are considered the last resort for the management of moderate-to-severe DED; ASEs are associated with difficulties in preparation and refrigeration and risks of contamination.[68] Human HSEs and USEs can be considered for patients who require serum eyedrops but are unable to provide their own blood because of logistical or clinical constraints.

Careful monitoring is essential to ensure patient compliance and to assess improvement in symptoms and signs. The timing of assessments for therapeutic success varies among different individuals and therapies.[69] Assessment after 1 to 3 months is recommended for most treatments, except CsA, which may require a longer duration to demonstrate therapeutic effects.[38,70,71] Patients with moderate DED may be examined every 6 weeks, whereas patients with severe DED may require more frequent monitoring (eg, every 2 to 3 weeks). Diagnostic tests, such as corneal fluorescein staining and TBUT, should be performed during follow-up visits to assess treatment response.[72-75] Patients with autoimmune disease–related DED, such as Sjogren syndrome and graft-vs-host disease, should be referred to specialists for further evaluation and treatment.

This systematic review focused on randomized controlled studies of five therapeutic options (HA, topical steroids, CsA, serum eyedrops, and lifitegrast) for moderate-to-severe DED, which is defined as a severity level of ≥2 according to the Dry Eye Workshop I grading scheme.[8] However, the scheme is not evidence-based and lacks objectivity and universality. A standardized classification system that can objectively categorize different severities of DED is necessary to facilitate personalized treatment strategies.

This systematic review had some limitations. Most included studies had short follow-up periods and relatively small sample sizes. According to the Grading of Recommendations, Assessment, Development, and Evaluations framework,[76] the quality of evidence for most included studies was moderate, owing to publication bias and corporate sponsorship. As a result, the findings should be interpreted with caution.

Contributors

Both authors designed the study, acquired the data, analyzed

the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. Both authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

Both authors have disclosed no conflict of interest.

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Data availability

All data analyzed during the present study are available from the corresponding author upon reasonable request.

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