Original Article

Cyclosporine Eye Emulsion Vs Loteprednol Etabonate Eye Drops for the Management of Subepithelial Infiltration Linked to Adenoviral Keratoconjunctivitis

PJO – Official Journal of Ophthalmological Society of Pakistan

Sura Luay Kadhim[1], Ziyad Kamel Al-Jenabi[2]
[1]Al Kindy College of Medicine Baghdad University, Baghdad, Iraq.
[2]College of Medicine, Babylon University, Babylon, Iraq

ABSTRACT

Purpose: To compare the effectiveness of cyclosporine eye emulsion versus Loteprednol etabonate eye drops in the management of subepithelial infiltrates **(**SEIs) secondary to adenoviral keratoconjunctivitis(AKC).

Study Design: Quasi experimental study.

Place and Duration of Study: Al-Kindy Teaching Hospital in Baghdad from January 2024 to December 2024.

Methods: Sixty-nine patients with confirmed multifocal SEIs were enrolled and assigned to either cyclosporine (n=35) or Loteprednol (n=34) group by convenient sampling. Patients were monitored over 6 months using slit-lamp biomicroscopy and non-contact tonometry to assess treatment outcomes, side effects, and recurrence. Data was analyzed using SPSS version 26. Descriptive statistics (frequency and percentage) were used for numerical data. The Chi-square test was applied to compare categorical variables such as age groups, gender distribution, side effects, and recurrence rates. Independent sample t-tests were used to compare continuous variables, including IOP between the groups. A p-value < 0.05 was considered statistically significant.

Results: Loteprednol demonstrated faster SEI clearance at 2 and 4 months (P < 0.05), with higher rates of complete corneal clarity by month 4. However, it also showed significant rise in IOP, and a higher recurrence rate (20.6%) compared to cyclosporine (8.6%) at 6 months. Cyclosporine was associated with more early ocular discomfort but offered better long-term control and lower relapse.

Conclusion: Loteprednol provides faster symptomatic relief, whereas cyclosporine offers more durable outcomes with fewer recurrences. Sequential therapy, starting with corticosteroids and transitioning to cyclosporine, may optimize AKC management and further investigation warrants.

Keywords: Cyclosporine, Loteprednol, Subepithelial infiltrates, Adenoviral, keratoconjunctivitis.

How to Cite this Article: Kadhim SL, Al-Jenabi ZK. Cyclosporine Eye Emulsion Vs Loteprednol Etabonate Eye Drops for the Management of Subepithelial Infiltration Linked to Adenoviral Keratoconjunctivitis. 2025;41(4):395-400. **Doi: 10.36351/pjo.v41i4.2160**

Correspondence: Ziyad Kamel Al-Jenabi
College of Medicine, Babylon University, Babylon, Iraq
Email: qaisajam1981@gmail.com

Received: July 16, 2025
Revised: September 5, 2025
Accepted: September 10, 2025

INTRODUCTION

Adenoviral keratoconjunctivitis (AKC) frequently leads to persistent subepithelial infiltrates (SEIs) that impair vision and cause discomfort. While corticosteroids like Loteprednol etabonate offer rapid relief, they carry risks of raised intraocular pressure (IOP) and recurrence. Cyclosporine (CsA), an immunomodulatory agent, offers an alternative with potentially better long-term outcomes.

AKC is a highly contagious ocular infection caused predominantly by human adenovirus serotypes D8, D37, and D19.[1] Clinically, it presents with redness, tearing, photophobia and, notably, the development of SEIs in the corneal stroma, occurring typically 1–2 weeks post-infection. These SEIs are granular

accumulations of immune cells that can persist and impair vision, provoking discomfort and astigmatism, and occasionally leading to permanent corneal scarring if left untreated.[1] SEIs represent immune-mediated sequelae rather than active viral replication.[2] Standard treatment is primarily supportive (lubricants, cold compresses), yet persistent or symptomatic SEIs often prompt anti-inflammatory intervention.[3] Corticosteroids, especially Loteprednol etabonate, are commonly used due to their efficacy in reducing inflammation and improving comfort and visual acuity.[4] Loteprednol boasts a favorable safety profile among ocular steroids, as it undergoes rapid local metabolism, reducing the risk of high IOP.[5] However, the main drawback is the potential for viral reactivation during steroid use and relapse upon tapering.[6] To address steroid-related concerns, immunomodulatory agents like topical CsA have emerged as alternative or adjunctive therapies.[7]CsA functions as a calcineurin inhibitor, attenuating T-cell activation and inflammatory cytokine release without causing the same level of local immunosuppression as corticosteroids.[7]

Several clinical studies have explored CsA in AKC-associated SEIs. A prospective study of CsA 0.5% emulsion in 37 eyes found significant reduction in infiltrate density by day 15, improved visual acuity, and no serious adverse events, supporting its safety and efficacy.[8] There are other studies which have reported successful resolution of SEIs using CsA 1% eye drops, in cases resistant to steroids.[9,10]. Understanding the relative roles of Loteprednol and CsA, alone or in combination, is essential for crafting optimal, individualized treatment strategies. The aim of study is to assess the effectiveness of CsA eye emulsion against Loteprednol etabonate eye drops in facilitating the clearance of subepithelial infiltrates linked to AKC and to analyze their relative effects on the recurrence rate after treatment.

METHOD

This study was conducted from January 2024 to December 2024 to evaluate the efficacy of CsA eye emulsion versus Loteprednol etabonate eye drops in managing SEIs secondary to AKC. Patients were recruited from multiple private ophthalmology clinics across Baghdad, as well as from the specialized eye clinic and ophthalmology department at Al-Kindy Teaching Hospital. The study was approved by the Institutional review board/Ethical review board **(Ref no: 352)**.

A formula for comparing means and another for comparing proportions was employed. Assuming 76% vs. 37% success, α=0.05, and power=80%, the necessary sample size for clear cornea rates was approximately 24 per group; with 10–15% attrition, this number rose to approximately 27–28. Assuming SD=3 mmHg, Δ=2 mmHg, α=0.05, and power=80%, the necessary sample size for mean IOP was approximately 35 per group. With >80–90% power, the actual sample (34 and 35) either met or surpassed these goals. The study followed Declaration of Helsinki and patients gave verbal and written informed consent. Ethical approval was received from the local ethical committee (number 352 and date 1/4/2025). All patients presenting with clinically confirmed multifocal SEIs following AKC were included. Exclusion criteria comprised of patients with co-existing blepharitis, bacterial conjunctivitis, intraocular inflammatory diseases, or a prior diagnosis of glaucoma. Each patient underwent comprehensive ophthalmic evaluation using a slit-lamp biomicroscope (Chongqing Sun Kingdom, Model LS-4, manufactured on 2023/03/30). IOP was monitored using a Keeler Pulsair desktop non-contact tonometer (Model SL 44AA, UK) to detect potential steroid-induced ocular hypertension. Patients were assigned to either CsA eye emulsion or Loteprednol eye drops and followed up at 2 weeks, 2 months, 4 months, and 6 months to assess treatment outcomes.

Data was analyzed using SPSS version 26. Descriptive statistics (frequency and percentage) were used to summarize numerical data. The Chi-square test was applied to compare categorical variables such as age groups, gender distribution, side effects, and recurrence rates. Independent sample t-test was used to compare continuous variables, including IOP between the two groups. A p-value < 0.05 was considered statistically significant.

RESULTS

There were 62.3% patients within the age range of 20–39 years. The sample showed male predominance (55.1%). Out of total 69 patients, 35 received CsA and 34 received Loteprednol. The demographic data is shown in Table 1.

There was no statistically significant difference between the ages and gender of both groups.

Difference in the side effects of both drugs is depicted in Table 2.

Participants treated with Loteprednol had a significantly higher mean IOP (18.38 ± 2.31) than CsA (15.57 ± 3.06) with p value of 0.0001.The difference was statistically and clinically significant, suggesting Loteprednol carries a higher risk of steroid-induced ocular hypertension. Regular monitoring of IOP is advisable in patients receiving Loteprednol therapy.

Table 3 shows follow up clinical findings. After 2 weeks, CsA showed a higher rate of infiltrate size reduction (88.6%) as compared to Loteprednol (64.7%) with P = 0.045. After 2 months, clear cornea was more frequent with Loteprednol (52.9%) than CsA (17.1%). However, CsA had more cases with reduced but still present infiltrates (68.6% with 2–4 infiltrates). Loteprednol showed better corneal clearance, while CsA maintained ongoing improvement.

After 4 months, 1–2 infiltrates were more commonly seen in CsA group versus Loteprednol group (57.1% vs. 23.5%, p = 0.003). After 6 months, clear cornea was achieved in both groups: 91.4% for

Table 1: *Demographic and Clinical Characteristics.*

Variables		Frequency	Percent
Age groups	*<20*	12	17.4
	20-29	23	33.3
	30-39	20	29.0
	40-49	14	20.3
Types of drugs	*CsA*	35	50.7
	Loteprednol	34	49.3
Gender	*Female*	31	44.9
	Male	38	55.1
Before treatment	*multifocal sub epithelial infiltrates*	69	100.0

Table 2: *Comparison of Age, Gender, and Local Side Effects Between Cyclosporine and Loteprednol Treatment Groups*

Age Group	Drug type		P-value
	Cyclosporine	Loteprednol	
<20	5 (14.3%)	7 (20.6%)	0.5
20–29	10 (28.6%)	13 (38.2%)	
30–39	11 (31.4%)	9 (26.5%)	
40–49	9 (25.7%)	5 (14.7%)	
Gender	**Cyclosporine**	**Loteprednol**	**P-value**
Female	15 (42.9%)	16 (47.1%)	0.8
Male	20 (57.1%)	18 (52.9%)	
Side effects	**Cyclosporine**	**Loteprednol**	**P-value**
Burning, discharge	14 (40.0%)	0 (0.0%)	**0.0001**
No side effects reported	12 (34.3%)	17 (50.0%)	
Redness, photosensitivity	0 (0.0%)	12 (35.3%)	
Tearing	9 (25.7%)	0 (0.0%)	
Transient blurring of vision	0 (0.0%)	5 (14.7%)	

Table 3: *Treatment Outcomes at 2 Weeks, 2 Months, 4 Months, and 6 Months for Cyclosporine and Loteprednol Groups.*

After 2 Weeks	Drug Type		P-value
	Cyclosporine	Loteprednol	
2–4 infiltrates	4 (11.4%)	12 (35.3%)	**0.045**
Decrease size of infiltrates	31 (88.6%)	22 (64.7%)	
After 2 Months	**Cyclosporine**	**Loteprednol**	**P-value**
2–4 infiltrates	24 (68.6%)	16 (47.1%)	**0.002**
Clear cornea	6 (17.1%)	18 (52.9%)	
Smaller size/No. of infiltrates	5 (14.3%)	0 (0.0%)	
After 4 Months	**Cyclosporine**	**Loteprednol**	**P-value**
Clear cornea	13 (37.1%)	26 (76.5%)	**0.003**
1–2 infiltrates	20 (57.1%)	8 (23.5%)	
2–4 infiltrates	2 (5.7%)	0 (0.0%)	
After 6 Months	**Cyclosporine**	**Loteprednol**	**P-value**
Clear cornea	32 (91.4%)	27 (79.4%)	**0.005**
1–2 infiltrates - recurrence	3 (8.6%)	0 (0.0%)	
1–2 infiltrates recurrence	0 (0.0%)	7 (20.6%)	

CsA, 79.4% for Loteprednol. Recurrence was seen in 3 cases of CsA and 7 cases of Loteprednol. Although Loteprednol achieved faster resolution, CsA had fewer recurrences, suggesting better long-term control.

Loteprednol provides faster symptomatic and clinical improvement, especially in the first 2–4 months. CsA is slower acting but more durable, with fewer long-term recurrences.

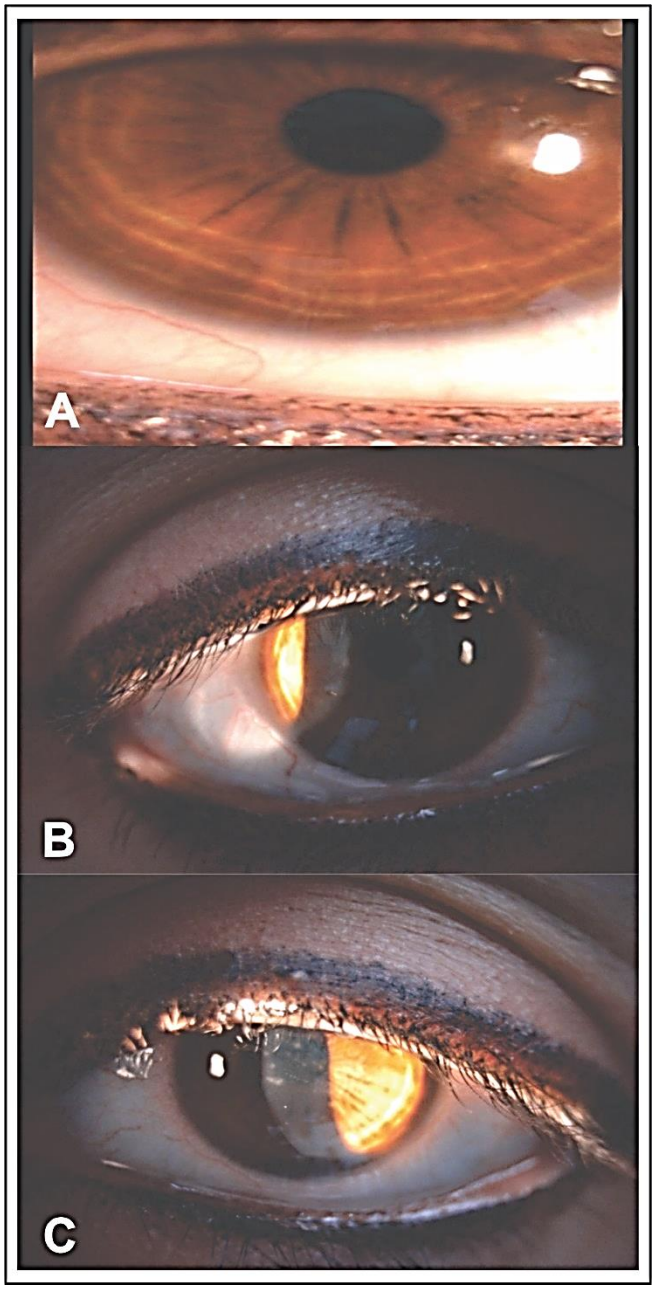

Figure 1a: Decrease in size and number of infiltrates. 1b: Multifocal subepithelial infiltrate. 1c: Clear cornea.

SEIs from AKC. Both groups had similar demographics, ensuring that outcomes were unlikely

DISCUSSION

In this study, the two topical treatments, CsA eye emulsion and Loteprednol etabonate drops, demonstrated distinct therapeutic profiles in managing to be influenced by age or gender disparities. However, differences in effectiveness, side effects, IOP and relapse rates were seen, holding practical significance for clinical decision-making. Loteprednol resulted in faster initial resolution: within two weeks, only 11.4% of CsA-treated patients had 2–4 visible infiltrates, compared to 35.3% in the Loteprednol group. The reduction in infiltrate size was also greater with CsA (88.6% vs. 64.7%, P = 0.045). Although Loteprednol's corticosteroid effect provides rapid resolution, this data suggests that CsA may drive early improvements more efficiently, potentially due to its immunomodulatory action on T lymphocytes and cytokine suppression.

A meta-analysis highlighted that CsA enables SEI improvement with minimal risk of recurrence often seen with steroid monotherapy.[11]An RCT compared topical Loteprednol etabonate 0.5% with CsA 0.05% in AKC-induced SEIs.[12] Both groups showed lesion resolution by week 12, but the steroid group achieved faster initial resolution (84% vs. 70% at four weeks). Crucially, the recurrence rate was higher in the steroid group (11.3% vs. 4.5%), suggesting CsA's advantage in preventing relapse.[12]Combined therapy, initial corticosteroid followed by CsA, has gained attraction to balance prompt alleviation with long-term control, although robust trials in AKC are lacking; evidence is extrapolated from dry eye studies where Loteprednol plus CsA improved tolerability and treatment outcomes.[13] Given the risk of IOP elevation, cataract formation and viral persistence with extended use of corticosteroids, CsA presents a safer long-term option. Yet, it acts more slowly and may be less effective in acute inflammation. Prior reports confirm the efficacy of both modalities in SEI reduction.[14-16]

At 2nd and 4thmonth, Loteprednol outpaced CsA in achieving complete corneal clarity. By month four, 76.5% of Loteprednol-treated eyes had a clear cornea, versus only 37.1% in the CsA cohort (P = 0.003). This aligns with literature noting corticosteroids' superior acute anti-inflammatory potency.[17] Nonetheless, corticosteroid monotherapy carries risks, our

Loteprednol group had significantly higher IOP, consistent with known steroid-induced ocular hypertension, even with "safer" steroids like Loteprednol.[16,18]This validates the necessity of regular IOP monitoring during steroid therapy. At six months, CsA exhibited a notable advantage in relapse prevention. Despite its slower initial action, CsA yielded a 91.4% clearance rate and only 8.6% recurrence, compared to 79.4% clearance and 20.6% relapse in the Loteprednol group (p = 0.005).

Previous observational studies of 0.05% CsA have shown similar relapse rates around 9–15%,[16] while steroid monotherapy often results in recurrence rates up to 20%.[19] This suggests CsA's advantage lies in establishing sustained immune regulation and lowering long-term relapse risk. Side effect profiles differed markedly. CsA induced more ocular surface discomfort (40% burning/discharge, 25.7% tearing/ redness), while Loteprednol was associated with redness/photosensitivity (35.3%) and transient blurring (14.7%). Notably, overall side effects were more common with Loteprednol (50% vs. 34.3%, P = 0.0001), likely due to its corticosteroid-associated ocular physiological changes. CsA has shown burning and stinging as primary tolerability concerns.[16] The contrasting profiles of these agents suggest a complementary therapeutic model: corticosteroids like Loteprednol may provide rapid symptomatic relief and earlier corneal clearance, while CsA contributes to durable resolution and lower relapse. Sequential or combined regimens, such as a short-term steroid followed by maintenance immunomodulation with CsA, might maximize benefit while minimizing corticosteroid risks. Indeed, similar strategies are supported in dry eye literature, with fixed-combination approaches showing improved tolerability and patient outcomes.[20]

Limitations of this study include moderate sample size and six-month follow-up period. Future randomized controlled trials should extend follow-up beyond one year and may explore combined versus monotherapy protocols. Additionally, evaluating varying CsA concentrations (e.g., 0.1% emulsion) or alternative immunomodulators (e.g., tacrolimus) may refine long-term management strategies.[21] Similarly, lack of dose/formulation variation, short follow-up, single-center design, possible bias from unmasked assessments, and low power for uncommon events are other limitations.

CONCLUSION

Loteprednol etabonate offers superior short-term efficacy for SEI resolution, but its use carries risk of high IOP and relapse risks. Alternatively, CsA emerges as a safer and more durable remedy, albeit with slower onset and more ocular surface discomfort. Tailored treatment, potentially beginning with brief corticosteroids followed by CsA maintenance, might strike the optimal balance between rapid relief and long-term control in AKC associated SEIs.

Funding: This study was not funded by any organization.

Patient's Consent: Researchers followed the guide lines set forth in the Declaration of Helsinki.

Conflict of Interest: Authors declared no conflict of interest.

Ethical Approval: The study was approved by the Institutional review board/Ethical review board **(Ref no: 352)**.

REFERENCES

1. **Chigbu DI, Labib BA.** Pathogenesis and management of adenoviral keratoconjunctivitis. Infect Drug Resist. 2018;**11:**981-993. Doi:10.2147/IDR.S162669.
2. **Al-Asmi M, Al-Busaidi A.** Nummular keratitis: A rare manifestation of brimonidine allergy. Oman J Ophthalmol. 2023;**17(1):**113-116. Doi:10.4103/ojo.ojo_99_23.
3. **Murray J, Stringer J, Hutt D.** Graft-versus-host disease (GvHD). In: Kenyon M, Babic A, editors. The European Blood and Marrow Transplantation Textbook for Nurses: Under the Auspices of EBMT. Cham (CH): Springer; 2018. Chapter 11. Available from: https://www.ncbi.nlm.nih.gov/books/NBK543657/ Doi:10.1007/978-3-319-50026-3_11. Accessed September 4, 2025.
4. **Beckman K, Katz J, Majmudar P, Rostov A.** Loteprednol Etabonate for the Treatment of Dry Eye Disease. J Ocul Pharmacol Ther. 2020;**36(7):**497-511. Doi:10.1089/jop.2020.0014
5. **Sheppard JD, Comstock TL, Cavet ME.** Impact of the Topical Ophthalmic Corticosteroid Loteprednol Etabonate on Intraocular Pressure. Adv Ther. 2016;**33(4):**532-552. Doi:10.1007/s12325-016-0315-8
6. **Blackwell J, Selinger C, Raine T, Parkes G, Smith MA, Pollok R.** Steroid use and misuse: a key performance indicator in the management of IBD. Frontline Gastroenterol. 2020;**12(3):**207-213. Doi:10.1136/flgastro-2019-101288.

7. **Yilmaz DE, Kirschner K, Demirci H, Himmerkus N, Bachmann S, Mutig K.** Immunosuppressive calcineurin inhibitor cyclosporine A induces proapoptotic endoplasmic reticulum stress in renal tubular cells. J Biol Chem. 2022;**298(3):**101589. Doi:10.1016/j.jbc.2022.101589
8. **Rhee MK, Mah FS.** Clinical utility of cyclosporine (CsA) ophthalmic emulsion 0.05% for symptomatic relief in people with chronic dry eye: a review of the literature. Clin Ophthalmol. 2017;**11:**1157-1166. Doi:10.2147/OPTH.S113437
9. **Gouider D, Khallouli A, Maalej A, Yousfi MA, Ksiaa I, Bouguerra C, et al.** Corticosteroids Versus Cyclosporine for Subepithelial Infiltrates Secondary to Epidemic Keratoconjunctivitis: A Prospective Randomized Double-Blind Study. Cornea. 2021;**40(6):**726-732. Doi: 10.1097/ICO.0000000000002589.
10. **Levinger E, Slomovic A, Sansanayudh W, Bahar I, Slomovic AR.** Topical treatment with 1% cyclosporine for subepithelial infiltrates secondary to adenoviral keratoconjunctivitis. Cornea. 2010;**29(6):**638-640. Doi: 10.1097/ICO.0b013e3181c33034.
11. **Tacelli M, Celsa C, Magro B, Barresi L, Guastella S, Capurso G, et al.** Risk Factors for Rate of Relapse and Effects of Steroid Maintenance Therapy in Patients With Autoimmune Pancreatitis: Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2019;**17(6):**1061-1072.e8. Doi: 10.1016/j.cgh.2018.09.051.
12. **Boynton GE, Raoof D, Niziol LM, Hussain M, Mian SI.** Prospective Randomized Trial Comparing Efficacy of Topical Loteprednol Etabonate 0.5% Versus Cyclosporine-A 0.05% for Treatment of Dry Eye Syndrome Following Hematopoietic Stem Cell Transplantation. Cornea. 2015;**34(7):**725-732. Doi: 10.1097/ICO.0000000000000436.
13. **Messmer EM, Ahmad S, Benitez Del Castillo JM, Mrukwa-Kominek E, Rolando M, Vitovska O, et al.** A panel of European dry eye disease experts. Management of inflammation in dry eye disease: Recommendations from a European panel of experts. Eur J Ophthalmol. 2023;**33(3):**1294-1307. Doi: 10.1177/11206721221141481.
14. **Jonas RA, Ung L, Rajaiya J, Chodosh J.** Mystery eye: Human adenovirus and the enigma of epidemic keratoconjunctivitis. Prog Retin Eye Res. 2020;**76:**100826. Doi: 10.1016/j.preteyeres.2019.100826.
15. **Peng W, Jiang X, Zhu L, Li X, Zhou Q, Jie Y, et al.** Cyclosporine A (0.05%) Ophthalmic Gel in the Treatment of Dry Eye Disease: A Multicenter, Randomized, Double-Masked, Phase III, COSMO Trial. Drug Des Devel Ther. 2022;**16:**3183-3194. Doi: 10.2147/DDDT.S370559.
16. **Rafe A, Tariq Munawar M.** Comparison of Steroid with Cyclosporine Eye Drops in Epidemic Keratoconjunctivitis. Pak J Ophthalmol.2020;**36(4)**. Doi:10.36351/pjo.v36i4.1085.
17. **Sheppard JD, Comstock TL, Cavet ME.** Impact of the Topical Ophthalmic Corticosteroid Loteprednol Etabonate on Intraocular Pressure. Adv Ther. 2016;**33(4):**532-552. Doi: 10.1007/s12325-016-0315-8.
18. **Feroze KB, Zeppieri M, Khazaeni L.** Steroid-Induced Glaucoma. 2023. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025 Jan. PMID: 28613653.
19. **Su S, Lei L, Fan Z, Zhang S, Wen Q, Wang J, et al.** Clinical Predictors of Relapse in a Cohort of Steroid-Treated Patients With Well-Controlled Myasthenia Gravis. Front Neurol. 2022;**13:**816243. Doi: 10.3389/fneur.2022.816243.
20. **Sheppard JD, Donnenfeld ED, Holland EJ, Slonim CB, Solomon R, Solomon KD, et al.**Effect of Loteprednol etabonate 0.5% on initiation of dry eye treatment with topical cyclosporine 0.05%. Eye Contact Lens. 2014;**40(5):**289-296. Doi: 10.1097/ICL.0000000000000049.
21. **Bhargava R, Kumar P.** Comparison of the safety and efficacy of topical Tacrolimus (0.03%) versus dexamethasone (0.05%) for subepithelial infiltrates after adenoviral conjunctivitis. Indian J Ophthalmol. 2019;**67(5):**594-598. Doi: 10.4103/ijo.IJO_1352_18.

Authors Designation and Contribution

Sura Luay Kadhim; *Ophthalmologist: Concepts, Design, Literature Search, Statistical Analysis, Manuscript Review.*

Ziyad Kamel Al-Jenabi; *Ophthalmologist: Data Acquisition, Data Analysis, Manuscript Preparation, Manuscript Editing.*