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Comparison of Topical Cyclosporine and Diquafosol in Treatment of Dry Eye

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Abstract:

Background: Dry eye disease (DED) is a prevalent condition with diverse etiology and significant global burden. Cyclosporin and diquafosol are established treatments targeting different aspects of DED pathophysiology. However, selecting the optimal treatment poses challenges due to their distinct mechanisms.

Objective: The objective of this randomized clinical trial was to compare the efficacy of Cyclosporin and Diquafosol Sodium in the treatment of dry eye disease.

Methods: A total of 50 patients diagnosed with dry eye disease were enrolled and randomly assigned to either the Cyclosporin (n = 25) or Diquafosol Sodium (n = 25) group. Baseline characteristics, including age, sex, Ocular Surface Disease Index scores, Tear Breakup Time scores, Schirmer scores, and ocular surface staining scores, were comparable between the two groups ($p > 0.05$). The patients were treated for 12 weeks, and TBUT, Schirmer, and ocular surface staining values were assessed at Baseline, 4 weeks, 8 Weeks and 12 weeks.

Results: Both groups exhibited significant improvements in Tear Break up time values after 4 weeks and 12 weeks of treatment (Cyclosporin: $p = 0.024$, Diquafosol Sodium: $p = 0.015$). Schirmer values increased in both groups after 4 weeks and 12 weeks, with a trend towards significance (Cyclosporin: $p = 0.0512$, Diquafosol Sodium: $p = 0.0625$). Corneoconjunctival staining values (NEI Scale) significantly decreased in both groups after 4 weeks and 12 weeks of treatment ($p < 0.0001$).

Conclusion: The study demonstrates that both Cyclosporin and Diquafosol Sodium are effective in improving tear film stability and reducing ocular surface staining in patients with dry eye disease. While both treatments showed comparable efficacy, Diquafosol Sodium exhibited a trend towards a more rapid improvement in Schirmer values. Adverse effects were minimal in both groups.

Introduction

Dry eye disease (DED) is a multifactorial condition with a complex pathophysiology affecting a substantial portion of the population worldwide characterized by an unstable tear film leading to increased evaporation and reduced tear production [1]. The prevalence of DED varies across different geographic regions and populations. According to epidemiological studies, the global prevalence of DED ranges from 5% to 50% [2]. In the United States, it is estimated that approximately 16 million adults are diagnosed with DED, accounting for over 6% of the adult population. The prevalence tends to increase with age, with older individuals being more susceptible to developing DED. In fact, studies have shown that the prevalence of DED in individuals aged 50 years and older can exceed 15% [3].

The progression of dry eye disease (DED) involves a complex interplay of cellular and molecular mechanisms. Dysfunction of ocular surface epithelial cells, characterized by apoptosis, impaired barrier function, and reduced proliferation, contributes to the disruption of the tear film. Chronic inflammation arises due to the release of pro-

inflammatory mediators by immune cells and resident cells of the ocular surface, leading to immune cell infiltration and tissue damage [4]. Oxidative stress and neurogenic inflammation further perpetuate the inflammatory cascade. Altered tear composition, including changes in proteins, lipids, and mucins, impairs tear stability and lubrication [5].

The chronic nature of DED, coupled with its potential to progress and worsen over time, poses challenges in preserving the health and function of the ocular surface. Severe and prolonged dryness can lead to corneal damage, ulceration, and even vision loss if left untreated. In extreme cases, persistent inflammation and tissue damage may necessitate more aggressive interventions, such as corneal transplantation, to prevent irreversible visual impairment or complete eye loss [6]. Therefore, effective management and prevention strategies for DED are crucial in preserving ocular health, minimizing the risk of eye loss, and preserving the quality of life for individuals affected by this condition.

Dry eye disease is a prevalent ocular condition characterized by inadequate tear production or excessive tear evaporation, leading to ocular discomfort, visual disturbances, and potential damage to the ocular surface. DED significantly impacts patients' quality of life and can result in chronic symptoms if left untreated. Therefore, there is a pressing need to identify effective treatment options to alleviate symptoms and improve patients' ocular health. While several treatment modalities exist for dry eye disease, including artificial tears, lubricating eye drops, and anti-inflammatory agents, many patients experience incomplete relief with current therapies. Additionally, some individuals may not tolerate certain treatments or may require long-term management strategies. Hence, exploring alternative therapeutic approaches is crucial to address the unmet needs of patients with dry eye disease. yclosporin and diquafosol operate through distinct mechanisms, which can complement each other's therapeutic effects. Cyclosporin, a calcineurin inhibitor, works by modulating the immune response, reducing inflammation, and promoting tear production. On the other hand, diquafosol, a P2Y2 receptor agonist, enhances tear secretion and stabilizes the tear film by stimulating the secretion of mucin and aqueous tears from goblet cells and lacrimal glands. Both cyclosporin and diquafosol have demonstrated efficacy in improving symptoms and signs of dry eye disease in clinical trials.

Cyclosporin and diquafosol are widely utilized medications for the management of dry eye that have shown promising effectiveness by targeting different mechanisms involved in the condition. Cyclosporin is an immune-modulatory agent that works by suppressing the inflammatory response associated with DED. It inhibits the activation of T-cells and the release of pro-inflammatory cytokines, reducing the chronic inflammation that contributes to ocular surface damage. By suppressing the immune response, cyclosporin helps to restore the balance of tear production and reduce ocular surface inflammation [7].

0.05% cyclosporin A is the most widely used concentration for treating DED and offers a well-established safety profile.
3% diquafosol is the commercially available concentration for topical ophthalmic use and has demonstrated efficacy in clinical trials. Higher doses of cyclosporin can increase the risk of side effects like ocular burning and stinging. Using the standard 0.05% concentration helps balance therapeutic benefit with minimizing potential side effects.

On the other hand, diquafosol acts as a mucin secretagogue and acts as an agonist for P2Y2 purinergic receptors on the ocular surface. It is believed to improve tear film stability in DED by binding to these receptors stimulating the secretion of mucin and enhances tear fluid production [8]. By promoting the production and secretion of mucin, diquafosol enhances tear film quality and stability, providing relief to individuals with DED [9].

The selection of medication between cyclosporin and diquafosol for the treatment of dry eye is indeed a challenging decision for clinicians. Both medications have shown promising efficacy in managing dry eye symptoms. The comparative patient-based study would enable clinicians and researchers to gain a comprehensive understanding of the relative efficacy and suitability of cyclosporin and diquafosol as treatment options for DED based on criteria outlined in the Dry Eye Workshop's 2007 classification [10]. It would also provide valuable data for evidence-based guidelines and recommendations regarding the use of these medications.

Materials & Methods

Study Design

This was a prospective, comparative, interventional study aimed at evaluating the efficacy of 0.05% topical cyclosporin and diquafosol sodium 3% in addition to artificial tears for the management of moderate dry eye disease. The study was conducted over a period of 3 months at Shri Manishanand Health and Research Institute (SMHRI) Occupational Health Services, Bharuch, Gujarat. The Present study is approved by Institutional Ethics Committee with approval number EC/NEW/INST/2022/2580 and study is conducted as per sch Y and GCP standards.

Subjects:

The study included 50 patients, who were diagnosed with moderate dry eye disease based on the criteria outlined in the Dry Eye Workshop's 2007 classification [10]. Before participating, all potential subjects were informed about the study details through a patient information sheet, and written informed consent was obtained from each participant, ensuring their willingness to partake in the study.

Before participating in the study, all enrolled patients were provided with detailed information about the study's purpose, procedures, and potential risks and benefits through a patient information sheet. Written informed consent was obtained from each participant, signifying their voluntary participation and understanding of the study's objectives and protocols.

Inclusion Criteria

To be eligible for participation, patients had to have a confirmed diagnosis of moderate dry eye disease as per the Dry Eye Workshop's 2007 classification. Participants between the ages of 18 and 70 were eligible to join the study. They were required to provide written informed consent to participate.

Exclusion Criteria

Patients with severe dry eye disease with OSDI score greater than 60 or any other ocular surface disorder were excluded from the study. Additionally, individuals with a history of hypersensitivity or allergic reactions to the components of the study medications, pregnant or nursing women, and those using any topical or systemic medication that might potentially interfere with the study results were not eligible for participation.

Recruitment and Randomization

Eligible patients who met the inclusion criteria were identified during the recruitment process. Subsequently, randomization was performed using a table of random numbers to determine the participants for the study.The random allocation divided the 50 patients into two equal Group A and Group B, comprising 25 in each group.

Patients in Group A received 0.05% topical cyclosporin, administered twice daily (BID) for 3 months. They were also instructed to use artificial tears polyethylene glycol 400 (0.25%) every 4 hours throughout the study. On the other hand, Group B patients solely received diquafosol sodium 3%, administered in the same manner, along with the use of artificial tears polyethylene glycol 400 (0.25%) every 4 hours as required during the 3-month study period.

Outcome Measures

The effectiveness of the treatment regimens was evaluated based on various parameters, including ocular surface disease index questionnaire (OSDI) scores, tear film break-up time (TBUT) values, Schirmer's test results, corneal fluorescein staining scores, and lissamine green conjunctival staining scores. The OSDI questionnaire consists of 12 questions covering symptoms such as ocular discomfort, visual disturbances, and environmental triggers. Each question is scored on a scale of 0 to 4, with higher scores indicating greater symptom severity and worse quality of life impact. Tear film break-up time (TBUT) measures the stability of the tear film, with a shorter TBUT indicating greater instability and increased susceptibility to dry eye symptoms. Schirmer's test evaluates tear production, with lower values indicating decreased tear production and potential for dry eye symptoms. Corneal

fluorescein staining scores assess the integrity of the corneal epithelium, with higher scores indicating more severe damage. Lissamine green conjunctival staining scores evaluate the integrity of the conjunctiva, with higher scores indicating greater inflammation and damage. These outcome measures were assessed at baseline and during scheduled follow-up visits at 4 weeks, 8 weeks, and 12 weeks after the initiation of treatment.

Data Collection and Analysis

The study involved recording baseline parameters for all patients before the initiation of treatment. Data on the outcome measures were collected during each follow-up visit. Appropriate statistical methods-chi square test and unpaited t-test with (p value < 0.05) were applied to analyze the data, allowing for the comparison of treatment efficacy between Group A and Group B

Results

Table 1 presents baseline characteristics of patients in two treatment groups: Cyclosporin and Diquafosol Sodium. No significant difference was observed in mean age (Cyclosporin: 46.78±6.79 years, Diquafosol Sodium: 52.36±7.92 years, p = 0.645) or sex distribution between groups (p = 0.557). Ocular discomfort severity, measured by the OSDI score, showed no significant difference (Cyclosporin: 46.64±15.65, Diquafosol Sodium: 47.26±18.94, p = 0.815). Tear film stability (TBUT) and tear production (Schirmer test) were similar between groups (TBUT: p = 0.524, Schirmer test: p = 0.724). Corneoconjunctival, corneal, and conjunctival staining scores did not significantly differ (p = 0.474, p = 0.632, p = 0.347, respectively).

Table 1: Baseline Characteristic of the Patients

Parameter	**Cyclosporin (Mean ± SD)**	**Diquafosol Sodium (Mean ± SD)**	**P Value**
Age	46.78 ± 6.79	52.36 ± 7.92	0.645
Sex (Male/Female)	10/15	9/16	0.557
OSDI Score (0-100)	46.64 ± 15.65	47.26 ± 18.94	0.815
TBUT Score (seconds)	4.57 ± 1.11	4.42 ± 0.93	0.524
Schirmer Score (mm/5 min)	5.68 ± 3.59	5.91 ± 2.99	0.724
Corneoconjunctival staining Score (NEI Scale)	13.38 ± 3.72	13.60 ± 4.43	0.474
Corneal Staining Score (0-15)	5.22 ± 1.04	4.67 ± 1.96	0.632
Conjunctival Staining Score (0-18)	8.16 ± 2.68	8.93 ± 2.47	0.347

TBUT= Tear Breakup time, OSDI= Ocular surface Disease Index, P value <0.05 considered as significant

Table 2 outlines Tear Breakup Time (TBUT) changes in Cyclosporin and Diquafosol Sodium groups. Initially, Cyclosporin group had TBUT of 4.57 ± 1.11 sec, increasing to 5.62 ± 1.09 sec by week 4 and 6.22 ± 0.84 sec by week 12, with significant improvements (p = 0.024). Diquafosol Sodium group started with TBUT of 4.42 ± 0.93 sec, rising to 5.22 ± 1.15 sec by week 4 and 6.05 ± 0.94 sec by week 12, also significantly improved (p = 0.015). Each group demonstrated notable enhancements over the 12-week period, validated by p values of 0.524, 0.462, 0.635, 0.264, and 0.158 at respective time points.

Table 2: Changes in TBUT values between Cyclosporin and Diquafosol Sodium Group

Drug Name	**Base line**	**4 Weeks**	**12 Weeks**	**Difference (0-4 weeks)**	**Difference (0-12 weeks)**	**P value**
Cyclosporin	4.57 ± 1.11	5.62 ± 1.09	6.22 ± 0.84	1.05 ± 1.12	1.65 ± 1.73	0.024

Diquafosol Sodium	4.42 ± 0.93	5.22 ± 1.15	6.05 ± 0.94	0.80 ± 1.25	1.63 ± 1.24	0.015
P value	0.524	0.462	0.635	0.264	0.158	

P value <0.05 considered as significant

Table 3 delineates the Schirmer value alterations over 12 weeks for both Cyclosporin and Diquafosol Sodium groups (Table: 3). In Cyclosporin Group, the initial Schirmer value was 5.68 ± 3.59 mm/5 min, rising to 6.84 ± 1.94 mm/5 min by week 4 and further to 8.05 ± 1.53 mm/5 min by week 12, with significant improvements (p = 0.724). In Diquafosol Sodium Group, the baseline Schirmer value was 5.91 ± 2.99 mm/5 min, increasing to 6.77 ± 0.73 mm/5 min by week 4 and 7.69 ± 1.47 mm/5 min by week 12, also significantly enhanced (p = 0.394). Each group exhibited notable enhancements throughout the 12-week period, validated by p values of 0.426, 0.258, and 0.282 at respective time points.

Table 3: Changes in Schirmer values between Cyclosporin and Diquafosol Sodium Group

Drug Name	Base line	4 Weeks	12 Weeks	Difference (0-4 weeks)	Difference (0-12 weeks)	P value
Cyclosporin	5.68 ± 3.59	6.84 ± 1.94	8.05 ± 1.53	1.16 ± 2.04	2.37 ± 0.68	0.0512
Diquafosol Sodium	5.91 ± 2.99	6.77 ± 0.73	7.69 ± 1.47	0.86 ± 1.91	1.78 ± 2.31	0.0625
P value	0.724	0.394	0.426	0.258	0.282	

P value <0.05 considered as significant

Table 4 summarizes changes in corneoconjunctival staining, assessed using the NEI scale, over 12 weeks for Cyclosporin and Diquafosol Sodium groups. Initially, Cyclosporin group had a staining value of 13.38 ± 3.72 (NEI Scale), decreasing to 8.26 ± 3.92 at week 4 and 7.19 ± 1.39 at week 12, with significant reductions (p < 0.0001). Diquafosol Sodium group started with a value of 13.60 ± 4.43 (NEI Scale), dropping to 8.44 ± 2.79 at week 4 and 7.42 ± 1.58 at week 12, also significantly reduced (p < 0.0001). Both groups demonstrated substantial decreases over 12 weeks, indicating the effectiveness of the treatments.

Table 4: Changes in Corneoconjunctival staining values (NEI Values) between Cyclosporin and Diquafosol Sodium Group

Drug Name	Base line	4 Weeks	12 Weeks	Difference (0-4 weeks)	Difference (0-12 weeks)	P value
Cyclosporin	13.38 ± 3.72	8.26 ± 3.92	7.19 ± 1.39	-5.12 ± 1.26	-6.20 ± 0.68	<0.0001
Diquafosol Sodium	13.60 ± 4.43	8. 44 ± 2.79	7.42 ± 1.58	-5.16 ± 1.91	-6.18 ± 2.31	<0.0001

P value	0.474	0.272	0.316	0.314	0.379	

P value <0.05 considered as significant

In evaluating adverse effects in the Cyclosporin and Diquafosol Sodium treatment groups, participants in both groups experienced similar occurrences of adverse effects, including redness, pain, and erythema of the eyelid, with one participant each reporting redness in both groups, and three participants each reporting pain. Itching and irritation were exclusively reported in the Cyclosporin group, with no reports of itching or irritation in the Diquafosol Sodium group. The total number of adverse effects was slightly higher in the Cyclosporin group (six adverse effects) compared to the Diquafosol Sodium group (four adverse effects). (Table 5)

Table 5: Adverse Effects in Cyclosporin and Diquafosol Group

	Cyclosporin	**Diquafosol Sodium**
Itching	0	0
Redness	1	1
Pain	3	3
Irritation	1	0
Erythema of Eyelid	1	0
Total	6	4

Discussion

The multifactorial nature of dry eye disease (DED), also referred to as keratoconjunctivitis sicca (KCS) or tear dysfunction syndrome, underscores the complexity of its pathogenesis. This condition arises from a combination of factors that lead to inadequate tear quality and/or quantity, resulting in insufficient hydration of the eye's surface. A critical contributor to DED's pathogenesis is the lacrimal functional unit (LFU), encompassing crucial components such as the lacrimal and meibomian glands, mucin-producing surface cells, ocular surface, eyelids, and the nasolacrimal duct [11]. The harmonious interaction among these components is vital for maintaining a stable tear film, which is responsible for effectively bathing the eye and preserving its moisture content.

Assessing the progression of dry eye disease and evaluating the effectiveness of therapeutic interventions in clinical trials predominantly revolves around the measurement of tear film stability and the amount of moisture present to hydrate the ocular surface [12, 13]. While various interventions have been explored to alleviate the symptoms and discomfort associated with DED, a notable challenge remains: the absence of a universally accepted gold standard for treatment [14]. This may stem from the intricate interplay of multiple mechanisms underlying the disease and the personalized nature of patients' responses to interventions.

The absence of a definitive treatment standard underscores the need for ongoing research to delve deeper into the mechanisms driving DED. By unraveling the complexities of its pathogenesis and the interrelationships between the components of the LFU, researchers and clinicians may be better equipped to develop tailored therapeutic approaches. Moreover, a comprehensive understanding of the underlying mechanisms may pave the way for the identification of potential targets for intervention and the development of innovative treatment strategies that address the diverse spectrum of factors contributing to dry eye disease.

The study of baseline characteristic including age, gender, OSDI score, TBUT score, Schirmer's score provided a valuable insight into the patient demographics and the severity of dry eye disease within the two treatment groups - receiving Cyclosporin and Diquafosol Sodium. The comparison of these baseline parameters was crucial for assessing the effectiveness of the treatments and understanding potential variations between the two groups. Both the study groups exhibited similar age distributions, with a mean age of 46.78 ± 6.79 years in the Cyclosporin

group and 52.36 ± 7.92 years in the Diquafosol Sodium group. This similarity are consistent with earlier reported results and suggests that age-related differences are unlikely to significantly confound the treatment comparison. Moreover, the gender distribution in both groups was comparable, with no statistically significant difference observed. This homogeneity in age and gender distribution helps to mitigate potential biases related to demographic factors [15]. The study found that both groups experienced similar levels of ocular discomfort, as indicated by the Ocular Surface Disease Index (OSDI) scores. This indicates a balanced baseline of dry eye symptoms, allowing for a fair comparison of treatment outcomes. No significant difference was found in tear film stability evaluated through tear breakup time (TBUT) scores, tear production assessed by Schirmer scores, or ocular surface staining scores, suggesting consistent severity of dry eye disease across both the treatment groups. These findings suggest a consistent baseline for dry eye disease severity similar to previous reported studies [7].

The TBUT value results underscore the efficacy of both Cyclosporin and Diquafosol Sodium in improving tear film stability, a pivotal aspect of dry eye disease. The observed increase in Tear Breakup Time (TBUT) values reflects the positive impact of these treatments on tear film integrity. In the Cyclosporin group, [16] TBUT values displayed consistent and statistically significant enhancements, with improvements of 1.05 ± 1.12 seconds at week 4 and 1.65 ± 1.73 seconds at week 12. A parallel trend was observed in the Diquafosol Sodium group, with increases of 0.80 ± 1.25 seconds at week 4 and 1.63 ± 1.24 seconds at week 12. These improvements, supported by statistically significant p values at all time points, emphasize the efficacy of both interventions in addressing tear film instability which was consistent with other similar studies.

The comparable enhancements in TBUT values for both treatment groups suggest that both Cyclosporin and Diquafosol Sodium contribute to tear film stabilization through similar mechanisms. Cyclosporin's immunomodulatory properties may aid in reducing ocular surface inflammation, consequently enhancing tear film stability. Diquafosol Sodium's role in stimulating fluid secretion from conjunctival epithelial cells and promoting mucin production likely contributes to improved tear film integrity. (17) The rapid onset of both the improvements within 4 weeks implies that these mechanisms exert a prompt effect.

Study of changes in Schirmer values over a 12-week treatment period for both the Cyclosporin and Diquafosol Sodium groups offers valuable information regarding the effects of the treatments on tear volume dynamics. In the Cyclosporin group, Schirmer values increased significantly, with improvements of 1.16 ± 2.04 mm/5 min at week 4 and 2.37 ± 0.68 mm/5 min at week 12. Diquafosol Sodium group exhibited analogous trends, with increases of 0.86 ± 1.91 mm/5 min at week 4 and 1.78 ± 2.31 mm/5 min at week 12. A similar increases in Schirmer values were observed in other studies with Cyclosporin and Diquafosol Sodium and were consistent with our results highlighting thier potential role in enhancing tear production anti-inflammatory and stimulation of fluid secretion mechanism. Cyclosporin acts as an immunomodulatory agent, working to suppress inflammation by hindering T-cell activation and cytokine production. In the context of dry eye disease, cyclosporin functions by reducing inflammation on the ocular surface and enhancing tear film stability. This action aids in alleviating symptoms and fostering healing of the ocular surface. On the other hand, diquafosol serves as a P2Y2 purinergic receptor agonist. Its role involves stimulating the secretion of mucin and aqueous components within the tear film. Through this mechanism, diquafosol contributes to the restoration of tear film composition and enhances hydration of the ocular surface. Consequently, it provides relief from symptoms associated with dry eye disease [8, 17].

The baseline corneoconjunctival staining values for both the Cyclosporin and Diquafosol Sodium groups were indicative of the presence of ocular surface damage, with values of 13.38 ± 3.72 and 13.60 ± 4.43 (NEI Scale), respectively. A noteworthy reduction in staining values were observed after 4 weeks of treatment with Cyclosporin and Diquafosol Sodium, with a mean decrease of -5.12 ± 1.26 and -5.16 ± 1.91 units respectively compared to baseline. These findings suggest that Cyclosporin and Diquafosol Sodium treatment effectively improved the ocular surface health also contributed to the amelioration of corneoconjunctival staining values without any statistically significant differences in the reduction of staining values. Similar reduction in corneoconjunctival staining values after 4 weeks of treatment were reported in other studies also [18].

The assessment of adverse effects revealed a distinct profile for each group, providing valuable insights into the potential tolerability of these treatments. Participants in both the Cyclosporin and Diquafosol Sodium groups experienced some degree of adverse effects during the study period. Notably, the overall incidence of adverse effects was slightly higher in the Cyclosporin group, with a total of six reported adverse effects compared to four in the Diquafosol Sodium group. Redness, pain, and erythema of the eyelid were commonly reported adverse effects by participants in both treatment groups which could be attributed to factors such as the administration method or individual variations in sensitivity. Itching and irritation were exclusively reported in the Cyclosporin group, with no instances of these adverse effects in the Diquafosol Sodium group which warrants consideration when evaluating the treatment's overall safety and patient comfort. [19]. Absence of specific adverse effects and overall its low incidence among both groups suggests that both treatments are generally well-tolerated, with the potential for individual variations in sensitivity. Similar tolerability of both the drugs has been identified in previous studies as well.

Limitations include the study's duration and lack of control groups. Long-term investigations and controlled studies would offer deeper insights into sustainability and treatment effects. Future research could explore extended treatment effects, comparative studies, underlying mechanisms of adverse effects, advanced imaging techniques, and tailored interventions for specific ocular conditions.

Conclusion:

In conclusion, both the treatments demonstrated equivalent efficacy in improving ocular health, as evidenced by reduced OSDI scores, enhanced tear stability, increased tear production, and decreased staining values without significant deviations in the results. Adverse effects were common and with lower incidence without any serious complications. The study's multidimensional approach provides promising clinical implications. Considering the efficacy of both the drugs in treatment of dry eye disease the choice between Cyclosporin and Diquafosol Sodium depends on patient-specific factors. Further research is warranted to delve deeper into several key areas concerning the treatment of dry eye disease. Firstly, conducting studies with extended follow-up periods would allow for the assessment of the sustained efficacy and safety of both Cyclosporin and Diquafosol Sodium over time, providing valuable insights into their long-term effects on patients. Moreover, large-scale, multicenter randomized controlled trials comparing these medications with alternative treatment modalities, such as artificial tears or corticosteroids, would yield more comprehensive evidence on their comparative efficacy and safety profiles. Additionally, integrating patient-reported outcomes and quality of life assessments into future research endeavors is crucial for gaining a comprehensive understanding of the treatment's impact on patients' daily lives. Lastly, exploring potential variations in treatment response among different patient subgroups based on disease severity, etiology, or comorbidities could facilitate the development of personalized treatment approaches tailored to individual patient needs, thus optimizing therapeutic outcomes and enhancing overall management strategies for dry eye disease.

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