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THE EFFICACY AND SAFETY OF TOPICAL CYCLOSPORINE A AND ITS GENERIC EQUIVALENCY DEPORES EYE DROPS IN THE TREATMENT OF DRY EYE DISEASE (REVIEW)

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ABSTRACT

Dry eye disease (DED) is a complex condition that can result in significant vision complications. Analyzing systematic reviews of DED treatment contributes to selecting the most effective and safe drug. This review examines the efficacy of cyclosporine A and the generic Depores ophthalmic emulsion cyclosporine 0.05% (cyclosporine 0.05%, Deva Pharmaceuticals, Turkey) in the treatment of DED. A search for scientific information in PubMed, PubMed Central, The Cochrane Library, Google Scholar databases, and the Internet was carried out using keywords: dry eye disease, Cyclosporine A, Ikervis, Restasis, generic cyclosporine 0.05% ophthalmic emulsion, Depores. The literature cited in scientific articles was also reviewed. The analysis of scientific articles allowed us to conclude about the efficacy of the Restasis–Depores generic (cyclosporine 0.05%, Deva Pharmaceuticals, Turkey) for the treatment of patients with DED who have not yet had access to this treatment. Depores is now available in Georgia, bringing a novel treatment option to patients with severe DED. The study revealed a small number of clinical studies evaluating the efficacy and safety of generic cyclosporine 0.05% ophthalmic emulsion. Given the scarcity of research articles on this generic, it is necessary to study the results of its use in the treatment of DED in Georgia, which will help improve the quality of life with a diagnosis of dry eye.

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KEYWORDS: Restasis; Generic Cyclosporin A; Ikervis; Depores; dry eye disease.

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Dry eye disease (DED) affects hundreds of millions worldwide and is one of the most frequent causes of patient visits to eye care practitioners. According to worldwide surveys, DED affects 5%–50% of the population [55]. The rising incidence of DED has become one of the major public health concerns. The Artificial Tears Market size was estimated at USD 2.06 billion in 2023, USD 2.23 billion in 2024, and is expected to grow at a CAGR of 8.27% to reach USD 3.60billion by 2030 (Global Artificial Tears Market by Product Type (Cellulose-derived, Glycerin-derived, Oil-based Emulsion), Application (Contact Lens Moisture, Dry Eye Treatment), Delivery Mode - Forecast 2024-2030). Tughan Duran et al. (1921) noted in their article that DED is rising in public with the increase in the use of digital screens such as tablets, cell phones, computer screens, etc. which causes prolonged exposure to blue light. Also, an increase in refractive and cataract surgeries, global climate changes, and the prolonged lifetime in humankind rise the incidence of DED [18]. DED is a multifactorial disease of the tear film and ocular surface that can produce debilitating symptoms such as ocular pain, burning, dryness, foreign body sensation, and visual disturbances [6]. Moderate to severe DED is associated with significant pain, limitations in performing daily activities, reduced vitality, poor general health, and often depression [15]. The ocular surface (cornea, conjunctiva and meibomian glands), the lacrimal gland, and the neural connections between them together form the Lacrimal Functional Unit (LFU), which regulates tear production, composition, distribution and clearance to maintain a stable protective tear layer that is essential for maintaining corneal epithelial health. When the meibomian glands in the eyelids don't work properly, it can lead to dry eye syndrome. This causes an increase in tear osmolarity and levels of inflammatory substances in the tears, which can harm the outer layer of the eye, a condition known as keratoconjunctivitis sicca (KCS). In KCS, the cornea can change such as loss of protective surface layer, disruption, increased inflammation, hardening, and cell death [49]. Structural or functional damage to any component of the LFU can disrupt the integrity and function of the tear film, leading to DED [41]. These can reduce visual function and the increased shear force on the corneal epithelium can stimulate nociceptors sensitized by inflammation causing irritation and pain that may precede frank clinical signs. Therapy of keratoconjunctivitis sicca should be tailored to improve tear stability, normalize tear composition, improve barrier function and minimize shear forces and damaging inflammation to improve corneal epithelial health [49]. The first mention of the dry eye problem was recorded in 1550 BC in ancient Egyptian documents known as the Ebers Papyrus [24]. However, the discipline of ocular surface care didn't begin until the mid-1850s, when a mechanism of tear secretion was first proposed. The modern era of dry eye began in 1973 when Frank Holly explained the role of mucin in

tear film quality and stability [3, 26, 31]. Alteration of membrane-bound mucin expression on corneal and conjunctival epithelial cells and/or gel-forming mucin secretion by goblet cells (GCs) promotes ocular surface diseases and DED. Changes in the mucin layer may lead to enhanced tear evaporation eventually contributing to tear hyperosmolarity which has been associated with ocular surface inflammation. Inflammatory mediators in turn may hurt GCs differentiation, proliferation, and mucin secretion. This sheds new light on the nature of DED. As a contributor to ocular surface immune homeostasis, GC loss may contribute to impaired ocular surface immune tolerance observed in DED. A key factor in the pathogenesis of DED – inflammation, and the infiltration of T cells and proinflammatory cytokines into the ocular surface – is known to initiate a cascade of events that result in the progression of its signs and symptoms [3].

Baudouin C, Rolando M, Benitez Del Castillo JM, et al. (2019) comprehensively revisited the current knowledge on ocular surface mucin biology as well as the available diagnostic tools and treatment options to improve mucin-associated homeostasis. In particular, they detailed the potential link between mucin dysfunction and inflammation as part of the uncontrolled chronic inflammation which perpetuates the vicious circle in DED [6]. Contributors to DED include but are not limited to, lacrimal gland hypofunction, meibomian gland dysfunction (MGD), ocular surface inflammation, and corneal nerve dysfunction. Current DED treatments target some facets of the disease, such as ocular surface inflammation, but not all individuals experience adequate symptom relief [42]. Although the pathogenic mechanisms of DED have not been fully elucidated, ocular surface inflammation in DED has become an important focus. Therefore, there have been relatively more studies investigating the roles of immune factors such as ocular surface inflammatory cells and inflammatory mediators in DED in recent years. To increase our understanding of DED, the Tear Film & Ocular Surface Society (TFOS), a non-profit organization, launched the TFOS Dry Eye Workshop II (TFOS DEWS II) and developed TFOS DEWS II definition: *Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles* [44].

The TFOS DEWS II Pathophysiology Subcommittee reviewed the mechanisms involved in the initiation and perpetuation of dry eye disease. Its central mechanism is evaporative water loss leading to hyperosmolar tissue damage. Research in human disease and in animal models has shown that this, either directly or by inducing inflammation, causes a loss of both epithelial and goblet cells. The consequent decrease in surface wettability leads to early tear film breakup and amplifies hyperosmolarity via a Vicious Circle. Pain in dry eye is caused by tear hyperosmolarity, loss of lubrication, inflammatory mediators and neurosensory factors, while visual symptoms

arise from tear and ocular surface irregularity. Increased friction targets damage to the lids and ocular surface, resulting in characteristic punctate epithelial keratitis, superior limbic keratoconjunctivitis, filamentary keratitis, lid parallel conjunctival folds, and lid wiper epitheliopathy. Hybrid dry eye disease, with features of both aqueous deficiency and increased evaporation, is common and efforts should be made to determine the relative contribution of each form to the total picture. To this end, practical methods are needed to measure tear evaporation in the clinic, and similarly, methods are needed to measure osmolarity at the tissue level across the ocular surface, to better determine the severity of dry eye [12]. Françoise Brignole-Baudouin et al (2017) investigated correlations of the inflammatory HLA-DR marker with clinical signs and symptoms commonly used to assess DED severity. They found HLA-DR correlated significantly with CFS clinical signs and to a lower extent Schirmer's test and weakly with TBUT and symptom reporting questionnaires. HLA-DR was reported to be useful for monitoring anti-inflammatory efficacy treatments in DED, which was confirmed with the reduction of HLA-DR while on CsA treatment. Its expression by conjunctival cells has the potential to serve as a biomarker, bridging signs and symptoms in clinical research in DED, but there is still a need for additional validation studies [11]. According to van Setten G, et al. (2016) clinical evidence suggested the existence of phase-like recurring dry eye complaints that may be linked to seasonal environmental conditions. In survey-based study they examined the influence of seasonality in dry eye pathophysiology. The study confirms the seasonal enhancement of dry eye sensations and symptoms. Environmental characteristics such as cold and heat as well as wind were the most commonly cited triggering factors. Geographical differences do exist between the countries surveyed and the seasonal peak of complaints appears related to temperature and humidity. The main seasons of dry eye complaints in Europe were winter and summer. Such seasonal characteristics in ocular surface disease should be kept in mind when considering diagnosis and treatment as well when investigating the ocular surface [50]. Without appropriate and adequate treatment, the ocular surface becomes progressively damaged, and DED may exert a profound negative impact on the quality of life [57]. It is established that DED pathophysiology is centred on tear hyperosmolarity, inflammation, and epithelial damage. First-line treatments such as artificial tears provide some symptomatic relief; however, they fail to address the underlying cause of the disease, namely corneal inflammation. In these cases, inflammation-reducing treatment options are required. Currently, the methods of treating DED worldwide mainly include the application of ocular surface lubricants to protect the mucous membrane and the use of anti-ocular surface inflammation drugs, punctual plug placement to reduce tear loss, and physical therapy of the eyelids to restore the meibomian glands. However, various methods can only reduce but not completely eliminate the symptoms of DED [42]. Unlike milder forms of DED that

can be managed with tear substitutes, lubricant drops or gels for symptom relief, more severe forms of DED are driven by a vicious circle of inflammatory processes that need something more than artificial tears to dampen the disease. Corticosteroids can perform that function, but have a poor side effect profile (especially with chronic use), and risk raising patients' intraocular pressure or inducing cataract formation [48]. The combination of corticosteroids and azathioprine continued in use as standard therapy until the 1980s heralded a new era of immunopharmacology. This new approach was characterized by using drugs to regulate defined subpopulations of immunocompetent cells more selectively. From this new approach, in 1972, came Cyclosporine A (CsA) [8], a fungal metbolite extracted from Tolypocladium inflatum gams. Tolypocladium inflatum is an ascomycete fungus originally isolated from a Norwegian soil sample that, under certain conditions, produces the immunosuppressant drug ciclosporin [17]. CsA was the first transplant-specific drug developed to specifically target the effector T cells to prevent rejection. It was initially used as a systemic immunosuppressant to minimize rejection of solid organ transplants. The Food and Drug Administration (FDA) in 1983 approved CsA for patient use in the United States. Still used widely today, CsA changed the entire field of transplantation by significantly increasing the survival times of all transplanted organs. Over the past decades, the development of several new drugs continues to extend transplanted organ survival times and reduce systemic drug toxicity. These new drugs accomplish this by specifically targeting T-cell subsets and modulating interleukins and cytokines [9]. Cyclosporine is a non-ribosomal peptide containing d-amino acid. The water solubility of cyclosporine is low and its absorption by the cell is variable. In ophthalmology, topically applied CsA was first used to inhibit corneal allograft rejection in the 1980s and later in various inflammatoocular surface disorders (OSD) [40]. Cyclosporine A is an alternative treatment to artificial tears as it is an immunomodulatory agent that can cure DED or at least lower the daily usage of artificial tears. The first topical cyclosporine A commercially available in 2000 was Restasis [20, 21, 22.]. Cyclosporine can be given to the eye in the form of aqueous drops, but the low dissolution of cyclosporine limits its penetration. Emulsions provide the effective topical ophthalmic delivery system with the potential for sustained drug release. In Restasis, 0.05% castor oil is included in the water emulsion. Various other delivery systems are under investigation [47, 53]. It is known that the ophthalmic emulsion of the immunomodulator cyclosporine-A (CsA) has a positive effect on this condition but its' absorption to intraocular tissues is limited. Nanosuspension is a drug formulation that aims to increase the bioavailability. The use of drug nanosuspension is an universal formulation to increase the solubility of the drug by reducing the particle size and increasing the surface area of the drug particles in order to achieve higher drug absorption at the targeted tissues. The aim of the study conducted by T. Duran, et al. (2021) was to develop new CsA

nanosuspension formulations for a better intraocular absorption via ocular delivery and to investigate the intraocular absorption of the formulations by comparing them with two marketed ophthalmic emulsions (Restasis® and Depores®) which are accepted to be biosimilar. The effect and the distribution of ophthalmic microemulsion forms of CsA in ocular tissues have been investigated in various animal studies. Two type of CsA loaded Eudragit S100 nanosuspension (A and B) were prepared by the quasiemulsion solvent evaporation technique which is an easy, inexpensive, and readily scalable method to prepare nanoparticles. Drug formulations were applied to both eyes of 20 male Albino New Zealand rabbits with an interval of 12 hours for 14 days. Then, they investigated the potential of CsA loaded Eudragit S100 based nanosuspension formulations for ocular delivery of CsA by comparing them two marketed ophthalmic emulsion including Depores and Restasis. In vitro CsA release profile tests showed that CsA loaded Eudragit S100 based nanosuspension formulation without benzalkonium chloride (BAK) had higher CsA release in mean of percentage comparing two marketed ophthalmic CsA emulsions which had similar particle size and polydispersity index. However, nanosuspension B had a positive zeta potential which could be the reason of higher CsA release. Nanosuspension B contained much more amount of CsA (mg/ml) comparing Depores, Restasis, and nanosuspension A: Depores – 0,50±0,2; Restasis – 0,51± 0,2; Nanosuspension A – 0,52±0,3; Nanosuspension B – 0,54±0,2 [18].

Nanosuspension B was also found as the highest CsA concentration in aqueous humor with a good ocular tolerability profile. The nanosuspensions have ideal mean particle size range for ophthalmic applications with a positive surface charge. Besides, they enable corneal adhesion and they have good stability upon storage. Therefore, it is concluded that CsA loaded Eudragit S100 based nanosuspension which contains CsA is an ideal candidate for the treatment of the dry eye [18]. In a comparative, prospective, interventional study Singla S, Sarkar L, Joshi M, (2019) compared the efficacy of topical cyclosporine (Cs) 0.05% alone and topical Cs 0.05% with loteprednol 0.5% in patients with moderate dry eye. They concluded that combination therapy with topical loteprednol and Cs is significantly better than topical Cs alone on alleviating symptoms and signs in moderate dry eye patients [54]. An anionic oil-in-water emulsion incorporating CsA 0.05% – Trademark: Restasis® (Allergan, Inc, Irvine, California) was approved by the US Food and Drug Administration (FDA) in 2003 for the treatment of moderate-to-severe DED to increase tear production in patients with keratoconjunctivitis sicca [29].

Because CsA is a lipophilic drug, a formulation was developed in a cationic emulsion (CE) containing unpreserved 0.1% (1 mg/mL) CsA (CsA CE) (Trademark: Ikervis® (Santen SAS, Evry, France) to help improve its retention on the surface of the eye and increase its bioavailability [36, 59]. CsA CE was registered in 2015 in the European Union for the treatment of severe keratitis in adult patients with DED that has not improved despite treatment

with tear substitutes [30]. Ciclosporin-containing eyedrops – Ikervis, 1 mg/mL ciclosporin (Santen) – a cationic oil-in-water emulsion of ciclosporin, based on Santen's Novasorb technology is approved for the "treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes" [62]. Currently, topical ophthalmic CsA is available as a licensed commercial emulsion or is prepared by hospital pharmacies with concentrations ranging from 0.05 to 2%. Levy O, et al. noted that many of its pharmacological effects on the ocular surface are direct consequences of its ability to inhibit T ciclosporine activation and apoptosis. Topical CsA differs from topical steroids in its favourable local and systemic tolerability at the concentrations used. Most clinical studies have evaluated topical CsA in moderate to severe DED and demonstrated its efficacy for the improvement of signs and symptoms, thus providing the sole indication for market approval and treatment protocols [40]. Current management is suboptimal and includes artificial tear supplementation and short-term use of topical steroids in severe cases. The recent approval of cyclosporine has transformed management strategies of severe DED and moderate-to-severe OSD. Topical cyclosporine, an immunomodulatory agent, can effectively inhibit T cells and cell-mediated inflammatory pathways, thus reducing the symptoms of DED and restoring the ocular surface [33]. Numerous clinical studies have shown that instillations of cyclosporine into the conjunctival cavity contribute to an increase in total tear production, as well as recovery of the density of goblet cells in the conjunctiva of DED patients. Boboridis & Konstas (2018) summarised existing information on the efficacy, safety, and tolerability of the new cyclosporine formulation and presented their expert opinion: *Topical cyclosporine A represents a promising, novel medication for the management of DED, Meibomian gland dysfunction, and inflammatory OSD. It is primarily beneficial for those patients requiring topical immunomodulatory therapy. This topical formulation also has the potential to meaningfully improve the management of moderate-to-severe glaucoma therapy-related OSD. Currently there is limited published clinical data concerning the efficacy of topical cyclosporine. There are, however, theoretical advantages when comparing this cyclosporine formulation with other established commercial preparations. Future research is needed to delineate the precise role and value of this medication* [7]. The purpose of the review by de Oliveira RC, Wilson SE was to guide practitioners in using topical CsA to manage DED to improve patient satisfaction and quality of life. They came to the following conclusion: CsA has been shown to prevent T-cell activation and production of inflammatory cytokines—breaking the inflammatory cycle of DED and increasing the production of tears and conjunctival mucin-producing cells in patients with KCS. A minimum twice-a-day six-month course of CsA is recommended to assess efficacy in patients with KCS. Patients must understand that DED is a chronic disorder requiring long-term therapy in most patients. Concurrent adjuvant short-term

treatment with topical corticosteroids may reduce the side effects and speed up the response to topical CsA treatment. Long-term CsA treatment may delay or halt the progression of DED in some patients [45]. Chronic DED can often result in mechanical stress on the ocular surface—leading to continuous erosion and damage to corneal and conjunctival tissue. In a case series of patients with recurrent corneal erosions and refractory persistent epithelial defects, treatment with cyclosporine A 0.05% improved tear film stability, reduced recurrent corneal erosions, and completely healed areas of previous epithelial loss [43,51]. According to the above analysis, it is now well established that anti-inflammatory CsA improves the treatment outcomes of most patients with DED. In recent years, anti-inflammatory therapy has become a significant part of the complex approach to the treatment of patients with DES. Many studies and meta-analyses have been published that support the efficacy of cyclosporine in the management of DED [1, 4, 5, 13,16, 25, 32, 34, 35, 36, 37, 38, 40, 56, 58., 60].

The first US generic equivalent to Restasis® 0.05% cyclosporine ophthalmic emulsion (COE), a complex drug product, was approved by the US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) in February 2022 [20]. COE is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, or dry eye disease [21]. Generic COE should help to make a drug product with the same safety, efficacy, and quality as the reference-listed drug (RLD) available to the public at a lower cost. A milestone achievement of the science and research program in the U.S. Food and Drug Administration's Center for Drug Evaluation and Research (CDER) represents the approval of the first generic 0.05% cyclosporine ophthalmic emulsion (COE). It is a locally acting complex drug product indicated to increase tear production in patients whose production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. The approval of a generic COE should improve the availability of this complex drug product to U.S. patients. A generic cyclosporine 0.05% ophthalmic emulsion Depores (cyclosporine 0.05%, Deva Pharmaceuticals, Turkey) which became commercially available in Turkey in 2013 is now available in Georgia, bringing a novel treatment option to patients with severe keratitis in DED who, until now, had no access to this treatment option. Since information on the safety and efficacy of the active substance is already available from the reference medicine, companies producing generic medicines usually only need to provide information on the quality of medicine and demonstrate that the generic medicine produces the same levels of the active substance in the human body as the reference medicine. After they have been authorised, the authorities monitor the safety of generic medicines [19]. Generic medicine contains the same active substance as the reference medicine, and it is used at the same dose(s) to treat the same disease. However, a generic medicine's inactive gradients, name, appearance

and packaging can be different. Generic medicines are manufactured according to the same quality standards as all other medicines evaluated the efficacy and safety of this generic CsA 0.05% in chronic dry eye patients. However, many ophthalmologists are concerned about the clinical performance of generic products because of the different pathways that generic and branded ophthalmic medications follow to gain approval [10]. Based on this concern, the study conducted by Cemile Banu Cosar et al. (2022) addresses an important issue regarding the clinical performance of a generic CsA 0.05%, ophthalmic emulsion (Depores, Deva Pharmaceuticals, Turkey) and demonstrates its' efficacy and safety. Thirty patients with dry eye disease were included in this observational, prospective study. The inclusion criteria were age >18 years and symptomatic dry eye disease in which artificial tears and gels were not sufficient. When initiating dry eye treatment, cyclosporine A was combined with loteprednol etabonate. Patients received topical CsA %0.05 (Depores, Deva Pharmaceuticals, Turkey) twice daily and artificial tears (sodium hyaluronate) as needed. Topical loteprednol 0.5% (Lotemax, Bausch and Lomb, USA) was given for 4 weeks, started as QID for the first 2 weeks and BID for the following 2 weeks. Compliance with the treatment regimen was assessed by patient interview at each visit. Of the thirty patients, 22 (73.3%) were females and 8 (26.7%) were males. The average age was 47.3 ± 1.4 (34- 64) years. The most common adverse event reported was ocular burning (6.7%), followed by stinging (3.3%), conjunctival hyperemia (3.3%), foreign body sensation (3.3%), and visual disturbance (3.3%). No other adverse effects were noted. It is concluded that Depores ophthalmic emulsion twice-a-day with loteprednol etabonate on initiation treatment has well-tolerability and improves subjective and objective measures of dry eye disease [14]. Cemile Banu Cosar et al. mention that in multicenter, randomized, double-masked Phase 3 study of Restasis, treatment with CsA 0.05% gave significantly greater improvements than vehicle in two objective signs of dry eye disease (corneal staining and categorized Schirmer values). CsA 0.05% treatment also gave significantly greater improvements in three subjective measures of dry eye disease (blurred vision, need for concomitant artificial tears, and the physician's evaluation of global response to treatment). The results of this Depores study are consistent with Phase 3 study of Restasis. Cemile Banu Cosar et al found that treatment with Depores significantly improves all subjective and objective parameters including corneal staining, Schirmer values, blurred vision, need for concomitant artificial tears, and the physician's evaluation of global response to treatment. Cemile Banu Cosar et al. admit that the use of loteprednol acetate on initiation treatment for a month might have played an enhancing role in improvement of signs and symptoms of DED [14]. In a prospective, double-masked, multicenter randomized controlled trial, 0.5% loteprednol therapy two weeks before the initiation of long-term topical 0.05% cyclosporine provided more rapid improvement than topical cyclosporine or artificial tears alone [52]. To compare the

clinical efficacy of two different doses of topical cyclosporine A used in addition to artificial tears in the treatment of patients with meibomian dysfunction and secondary dry eye. Fifty patients aged 18 to 40 years, who presented to the clinic between June 2020 and June 2021 were included in the study. Patients were divided into two groups: 25 patients were started on topical cyclosporine A 0.05% (Depores, DEVA, Turkey) twice a day and constituted Group A. Other 25 patients who were given topical cyclosporine A 0.1% (Depores X, DEVA, Turkey) once a day and were evaluated as Group B. Routine ophthalmological examinations were performed at the first- and third-month controls in both groups. No significant difference was observed between the two groups in terms of age and gender distribution. Cyclosporine A 0.05% and 0.1% eye drops were both seen to be effective in managing dry eye disease in patients with meibomian gland dysfunction in addition to artificial tears [2].

Each time a generic drug is released on the market, doctors evaluate the risk versus the reward to patients. In the end, the goal is safety, relief from symptoms, and overall satisfaction. The studies address an important issue regarding the clinical performance of a generic CsA ophthalmic emulsion and demonstrate its' efficacy safety and well-tolerability (Restasis – Depores generic (cyclosporine 0.05%, Deva Pharmaceuticals, Turkey) for the treatment of patients with DED who have not yet had access to this treatment [63].

Depores can also be used in dry eye seasonal and atopic keratoconjunctivitis. [https://ilac-kullanma-talimat.web.tr/depores-x-yuzde0-1-goez-damlasi-emuelsiyon-154084/kullanma-talimati]. Adenoviruses are the most common viruses causing acute viral infection of the conjunctiva, accounting for up to 75% of all conjunctivitis cases. The most frequent manifestation of ocular adenoviral infection is epidemic keratoconjunctivitis (EKC) [28]. Subepithelial infiltrates secondary to adenoviral keratoconjunctivitis arise from the immune reaction against the virus. As a result of multifocal subepithelial infiltrates (SEIs), in up to 50% of severe cases, decreased visual acuity is generally observed. The adenoviral keratoconjunctivitis infiltrates may be a source of significant visual impairment justifying the use of various therapeutic means. Topical steroids are effective in the treatment of SEI; however, after stopping steroid eye drops, recurrences may develop, and the patient may become steroid dependent. With long-term treatment, side effects of steroids such as intraocular pressure (IOP) increase, and cataract can develop. Therefore, topical cyclosporine A (CsA) has been proposed as a means of long-term treatment of SEIs. Few studies have reported topical cyclosporine A to be effective in the treatment of subepithelial infiltrates [23, 27, 39, 46, 61].

Gouider D, Khallouli A, Maalej A, et al. compared efficiency and tolerance between topical 0.5% cyclosporine A (CSA) and fluorometholone (FML) for subepithelial infiltrates (SEI) complicating epidemic keratoconjunctivitis. They conducted a prospective double-blind randomized study involving 72 eyes with SEI. Thirty-eight eyes were treated with topical FML (FML group) and 34 eyes with CSA 0.5% eye drops (CSA group). Baseline characteristics of both groups

were similar (P > 0.05). After 3 months of the regimen, resolution of SEI was 3 times more observed in the FML group than that in the CSA group (P = 0.026). After 6 months, resolution of SEI was observed in 70% of the FML group and in 47% of the CSA group (P = 0.068). The recurrence of SEI was almost twice higher in the FML group than that in the CSA group (16% vs. 9%). FML was better tolerated during the first 3 months: a higher Schirmer test value (P = 0.0003), less burning on instillation (P = 0.242), and less conjunctival injection (P = 0.003). For the rest of the follow-up period, the 2 groups were comparable in tolerance. No ocular hypertension was noted. Treatment was considered successful in case of SEI reduction and visual acuity improvement. It was concluded that epidemic keratoconjunctivitis can evolve favorably under both FML and CSA. The effect of FML is faster and CSA is more durable with fewer recurrences. Both are safe therapeutic options for long-term control of SEI [23]. Zghal I, et al. conducted a prospective study of 37 eyes of 22 patients with adenoviral keratoconjunctivitis with subepithelial infiltrates treated with cyclosporine A 0,5% eye drop to evaluate the efficiency and safety of the use of cyclosporine A 0,5% eye drop in the treatment of subepithelial infiltrates. Cyclosporine A 0,5% was prepared from the injectable form of cyclosporine (Sandimmun®) and artificial tears. The cyclosporine A 0,5% was first administered at 4 drops per day for 15 days, then at a rate of 2 drops per day for a variable period ranging from 15 days to 6 months. At the end of follow, the final average visual acuity was 8/10 and corneal astigmatism average was of 0.75 diopter. The slit lamp examination showed a marked decrease in the number and density of subepithelial infiltrates from the 15th day. No local complications were observed in our patients. The average follow-up was 13 months. Topical cyclosporine A was recommended as an effective and well-tolerated alternative to corticosteroids in the subepithelial infiltrates occurring as sequelae of adenoviral keratoconjunctivitis [61].

Despite the existence of credible sources on the high efficacy and safety of Depores (cyclosporine 0.05%, Deva Pharmaceuticals, Turkey) it is desirable to study the results of its use in the treatment of DED in Georgia, which will help improve the quality of life patients with a diagnosis of dry eye disease.

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РЕЗЮМЕ

ЭФФЕКТИВНОСТЬ И БЕЗОПАСНОСТЬ МЕСТНОГО ПРИМЕНЕНИЯ ЦИКЛОСПОРИНА А И ДЕПОРЕСА В ЛЕЧЕНИИ ЗАБОЛЕВАНИЙ СУХОГО ГЛАЗА (ОБЗОР)

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Болезнь сухого глаза (БСГ) – многофакторное заболевание, которое приводит к значительным осложнениям для зрения. Анализ систематических обзоров лечения БСГ способствует выбору наиболее эффективного и безопасного препарата. Данный обзор изучает эффективность применения циклоспорина А и дженерика Depores - офтальмологической эмульсии cyclosporine 0.05% (cyclosporine 0.05%, Deva Pharmaceuticals, Turkey) при лечении БСГ. Проведён поиск научной информации в базах данных PubMed, PubMed Central, The Cochrane Library, Google Scholar и интернете используя основные ключевые слова: dry eye disease, Cyclosporine A, Ikervis, Restasis, generic cyclosporine 0.05% ophthalmic emulsion, Depores. Также была просмотрена цитированная в научных статьях литература. Исследование выявило небольшое количество клинических исследований, оценивающих эффективность и безопасность 0,05%-й офтальмологической эмульсии дженерика циклоспорина.

Анализ научных статей позволил сделать вывод об эффективности дженерика Restasis – Depores (циклоспорин 0,05%, Deva Pharmaceuticals, Турция) для лечения пациентов с БСГ.

Учитывая скудность исследований данного дженерика, желательно изучить результаты его применения при лечении БСГ в Грузии, которые до сих пор не имели доступа к этому лечению, что поможет улучшить качество жизни с диагнозом «сухого глаза» в Грузии.

Keywords: Cyclosporin A; Restasis; Ikervis; Depores; dry eye disease.


depores
cyclosporine 0.05%
depores free
cyclosporine 0.05%
Steril
Depores %0.05
Oftalmik Emülsiyon İçeren Tek Dozluk Flakon
Siklosporin
Göze damlatılarak uygulanır
50 Flakon
Depores %0.05
Oftalmik Emülsiyon İçeren Tek Dozluk Flakon
Steril
Depores Free
% 0,05
Göz Damlası, Emülsiyon
Siklosporin
Göze damlalarak uygulanır
5.5 ml

რეზიუმე

ციკლოსპორინ A-ს და დეპორესის ადგილობრივი გამოყენების ეფექტურობა და უსაფრთხოება მშრალი თვალის დაავადების მკურნალობაში (მიმოხილვა)

პაპავა მ.ვ.[1]; გაფრინდაშვილი ნ.ჯ.[2]

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მშრალი თვალის დაავადება ფართოდაა გავრცელებული მთელ მსოფლიოში. არსებობს მრავალი კვლევა და მტკიცებულება აღნიშნული ნოზოლოგიის მართვისა და მკურნალობისათვის. მათ შორისაა ციკლოსპორინ -ს და ჯენერიკული ციკლოსპორინის ემულსიის - დეპორესის (Depores, cyclosporine 0.05%, Deva Pharmaceuticals, Turkey) ადგილობრივი გამოყენების ეფექტურობისა და უსაფრთხოების შესახებ მონაცემები მშრალის თვალის დაავადების დროს. ლიტერატურის მოკვლევა წარმოებდა PubMed, PubMed Central, The Cochrane Library, Google Scholar, და ინტერნეტში შემდეგი საძიებო ტერმინების გამოყენებით: dry eye disease, Cyclosporine A, Ikervis, Restasis, generic cyclosporine 0.05% ophthalmic emulsion, Depores. ამ სტატიით შესაძლებელია დავადასტუროთ ციკლოსპორინის სხვადასხვა ფორმულირებისა და დეპორესის (ციკლოსპორინი 0.05%, Deva Pharmaceuticals, თურქეთი) სარგებელი/რისკის პროფილი საქართველოში ხელმისაწვდომი მედიკამენტის - დეპორესის სასარგებლოდ მშრალი თვალის დაავადების სამკურნალოდ. ეს კი, უზრუნველყოფს მკურნალობის ახალ, ეფექტურ ვარიანტს საშუალო და მძიმე ხარისხის მშრალი თვალის მქონე პაციენტებისთვის, რომლებსაც დღემდე შეზღუდული წვდომა ჰქონდათ აღნიშნულ სამკურნალო საშუალებაზე.

საკვანძო სიტყვები: მშრალი თვალის დაავადება, Cyclosporin A, Restasis, Ikervis, Depores, დეპორესი.