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Clinical Implications of Seawater in Reducing MMP-9 Levels in Eye Disorders: A Clinical Trial in Allergic Conjunctivitis

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Abstract

Background: Allergic conjunctivitis is one of the most common allergic manifestations, affecting 20% of the global population. Elevated tear levels of matrix metalloproteinase 9 (MMP-9) have been correlated with the severity and chronicity of clinical manifestations of the disease. All current treatments, especially the most effective ones, are associated with side effects upon chronic administration. A natural treatment alternative without side effects that reduces pharmacodependence would be an excellent therapeutic option. This study aims to evaluate the anti-inflammatory efficacy of isotonic seawater solution on MMP-9 levels in the tears of patients with allergic conjunctivitis. **Methods:** This is a prospective study in which a total of 50 patients and 100 affected eyes were followed over time. Initial inclusion criteria were positive InflammaDry® test in both eyes + grade I, II, and III allergic conjunctivitis - Bonini-Gokhale scale. All patients were treated exclusively with Quinton® Eye Health, an isotonic seawater solution, six times a day for four weeks. **Results:** The InflammaDry test was positive in 100% of patients and eyes before treat-

ment as an inclusion criterion. After seawater treatment, 100% of patients and eyes with grade I conjunctivitis tested negative with undetectable MMP-9 levels in both eyes, 89% with grade II conjunctivitis, and 80% of patients with grade III. These changes are statistically significant. **Conclusion:** Seawater washes are a safe and highly effective treatment in reducing ocular surface inflammation in allergic conjunctivitis, being able to negate previously positive MMP-9 tear levels in an average of 89% of cases.

Keywords

Allergic Conjunctivitis, InflammaDry® Test, Seawater, Isotonic Ophthalmic Solution, MMP-9 Tear Level, Ocular Surface Inflammation, Deep Seawater

1. Introduction

The conjunctiva and tears serve as the primary defense barrier against pathogens on the ocular surface [1]. When an allergen comes into contact with the ocular surface, the immune system is activated, leading to either a mild response (in a healthy conjunctiva) or a hypersensitive response (in an allergic conjunctiva) [1].

Ocular allergy represents a group of hypersensitivity disorders that primarily affect the conjunctiva caused by the eye's response to environmental allergens [2] [3], affecting between 10% and 20% of the population [3]. With the global increase in allergy rates, it is estimated that around 20% of people suffer from some form of allergy, and between 40% and 60% of allergic patients experience ocular symptoms [3]. Although this condition generally does not affect vision, it can significantly reduce quality of life [3] due to the multiple symptoms associated with it, including itching, a foreign body sensation, serous or mucous discharge, conjunctival redness, and inflammation of the inner surface of the upper eyelid [3]. In severe cases, if conjunctivitis affects the cornea, it can cause scarring that compromises vision [3].

Allergic conjunctivitis is typically a bilateral inflammation of the conjunctiva that often becomes chronic or recurs periodically. It is a condition characterized primarily by an IgE-mediated response of the ocular surface to various allergens, such as grass/tree pollen, animal/pet dander, mold spores, or house dust mites [4]

The classification of allergic conjunctivitis has recently been updated by the Ocular Allergy group of the European Academy of Allergy and Clinical Immunology (EAACI) in order to distinguish two main types of hypersensitivity disorders affecting the ocular surface: ocular allergy and ocular non-allergic hypersensitivity. Ocular allergy can be caused by mechanisms either mediated or not mediated by IgE [5]. IgE-mediated ocular allergies include conditions such as seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), and atopic keratoconjunctivitis (AKC). Non-IgE-mediated forms include contact blepharoconjunctivitis (CBC), as well as VKC and AKC [3] [5]. Conversely, ocular non-allergic hypersensitivity includes conditions such as

giant papillary conjunctivitis (GPC), irritative conjunctivitis, irritative blepharitis, and other borderline or mixed forms [3] [5].

SAC and PAC are the most prevalent forms of allergic conjunctivitis, accounting for more than 95% of ocular allergy cases in the United States [3]. Their names refer to the timing of symptoms. SAC is an acute condition caused by outdoor allergens, such as grass pollens, and typically appears during certain seasons, varying with climate and time of year. PAC is a chronic condition with periods of exacerbation and remission, usually triggered by indoor allergens like dust mites or pet dander. The key difference between SAC and PAC lies in the frequency of symptoms: SAC flares up in warmer months, from spring to fall, and subsides during colder months, whereas PAC occurs year-round and tends to be less severe [3].

VKC is a chronic inflammatory condition that primarily affects the upper tarsal or limbal conjunctiva. While the pathogenesis of VKC is primarily immune-mediated, there is evidence to suggest that hormonal or genetic factors may also contribute to the disease [3].

AKC is the ocular manifestation of atopic dermatitis. It is a chronic inflammatory condition involving not just the ocular surface but also the eyelids, making it a form of blepharokeratoconjunctivitis. While AKC is partly mediated by an IgE-dependent mechanism, around 45% of patients do not show hypersensitivity to common allergens [3]. AKC can lead to dry eye, which exacerbates itchiness and perpetuates conjunctival inflammation. Recent research suggests that microbial factors, particularly the colonization of the conjunctiva by Staphylococcus aureus, may also play a role in the disease's development [3].

While all types of allergic conjunctivitis share similar symptoms, such as itching, redness, and tearing, the underlying immune responses, both cellular and humoral, can vary significantly [1]. As an example, IgA and MMP-9 concentrations in SAC are usually increased when compared to other ocular allergy conditions [1].

In brief, the mechanism involved in allergic conjunctivitis is a type 1 allergic reaction [3]. In sensitized individuals, when the allergen comes into contact with the conjunctiva, Th2 cells release cytokines that induce immunoglobulin E (IgE) production by B cells [3]. The IgE binds to mast cells and the allergen, triggering the release of inflammatory mediators responsible for the symptoms [3] such as IL-2, IL-4, IL-5, IL-13, IFN-γ, RANTES, and eotaxin [1]. These cytokines trigger the upregulation of matrix-metalloproteinase-9 (MMP-9), which consequently affects the corneal barrier epithelium [6].

Matrix metalloproteinases are a family of enzymes that play crucial roles in inflammatory processes. Among them, MMP-9, also known as gelatinase B, is a zinc- and calcium-dependent enzyme involved in tissue remodelling by degrading types IV and V collagen within the extracellular matrix (ECM). This enzyme is essential for various physiological processes, including wound healing and bone growth. MMP-9 is notably upregulated in several inflammatory conditions, in-

cluding arthritis, cardiovascular and pulmonary diseases, as well as cancer [7].

During inflammation, MMP-9, along with other MMPs, is increased in various tissues and fluids, such as serum, saliva, synovial fluid, and tears, making it a valuable biomarker for inflammation. Specifically, MMP-9 has been extensively studied as an inflammatory biomarker in tear samples, where it is significantly overexpressed in various diseases associated with ocular inflammation and ocular surface pathologies [7].

Normal matrix metalloprotease 9 (MMP-9) levels in human tears range from 3 to 40 ng/ml. Elevated levels of the matrix metalloproteinase 9 in tears have been shown to play a significant role in the inflammation of the ocular surface in patients with dry eye as well as allergic conjunctivitis. There is a direct correlation with the severity of clinical symptoms, contributing to the persistence and chronicity of the disease [7]-[11] InflammaDry® is a non-invasive test that accurately, quickly, and easily measures tear MMP-9 levels, capable of identifying levels greater than 40 ng/ml, which are considered clinically significant in inflammatory ocular surface diseases [6] [12]-[14]. The InflammaDry® test is easy to perform in the clinic for large case series, with high specificity (94%) and sensitivity (85%) [14].

Nonpharmacologic treatments should always be the first step and should complement any topical treatments. Complete avoidance of allergens is the ideal approach, though it is often difficult to achieve [3].

Although artificial tears are primarily designed to alleviate signs and symptoms of dry eye, they have also been shown to provide benefits in managing SAC**.** In studies, the reduction of SAC signs, such as conjunctival hyperaemia (redness), and symptoms is likely due to the artificial tears diluting and washing away allergens from the eye [2]. Additionally, artificial tears can act as a protective barrier, preventing further allergen exposure by inhibiting the allergens from binding to the ocular surface [2] [15].

Previous studies have demonstrated the efficacy of seawater washes in other allergic conditions such as rhinitis and dermatitis [16]-[20]. They are also very effective in ocular conditions like dry eye syndrome, improving symptoms in 68% of cases and significantly reducing levels of pro-inflammatory molecules IL-1 and IL-6 in tears [21]. Additionally, they reduce previously positive MMP-9 levels in 43% of cases [22]. Furthermore, seawater can drastically reduce tear IgE levels in vernal keratoconjunctivitis (VKC) by nearly 56% [23].

The aim of this study is to establish the anti-inflammatory efficacy of isotonic seawater washes on the ocular surface, demonstrating their ability to negativize and render undetectable previously positive MMP-9 tear levels in patients with allergic conjunctivitis.

2. Materials and Methods

2.1. Study Design

This is a prospective multicentre study registered with Clinical Trial Gov/USA NCT 04695795. It was conducted during the spring months of March, April, and

May of 2022 2023, and 2024, which is the period of highest activity for allergic conjunctivitis. This multicentre study was conducted at various medical and ophthalmological centres in the cities of Valencia and Albacete, Spain. The study protocol was approved by the ethics committee of the University of Valencia and was always subject to the principles of the Declaration of Helsinki. All patients signed specific and detailed informed consent forms before starting the study. In the case of minors under 18 years of age, legal guardians provided authorization.

2.2. Subjects, Inclusion and Exclusion Criteria

Inclusion criteria were patients with any type of active allergic conjunctivitis—acute seasonal allergic conjunctivitis (SAC), perennial-chronic allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC)—whether they had previously positive or negative skin prick tests (SPT) for airborne allergens, and with mild (I), moderate (II), or severe (III) clinical activity in both eyes, excluding blinding severity, as detailed in Table 1. Additionally, a positive InflammaDry test in both eyes was required for inclusion in the study.

Table 1. Type grading of conjunctivitis (adapted from the Bonini-Gokhale scale) [24] [25].

Grading	I Mild	II Moderate	III Severe	IV Blinding
Bulbar Conjunctiva	Congestion	Congestion	Trantras	Granuloma
Tarsal Conjunctiva	Micropapilla	Macropapilla 1 - 3 mm	Giant > 3 mm	Cobblestone
Corneal Staining	------	Microstaining	Macrostaining	Shield ulcer
Limbal Involvement	------	<180 degrees	>180 degrees	Limbal insufficiency, pannus, vascularization, corneal

Exclusion criteria were applied to ensure the validity and consistency of the results. Participants were excluded if they exhibited any of the following conditions: a negative InflammaDry® test in either eye before starting treatment, allergic conjunctivitis with significant asymmetry between the eyes, any other type of conjunctivitis (especially bacterial or viral), any form of blepharitis and other eyelid or lacrimal pathway pathologies, especially Meibomian gland dysfunction (MGD) or styes/chalazions. Additionally, patients with dry eye disease were excluded if they had a Schirmer test without anaesthesia > 10 mm and a tear film breakup time (TBUT) > 10 seconds in both eyes. Those who received any topical ocular treatment (including lubricants, ocular washes, antihistamines, mast cell stabilizers, corticosteroids, ocular decongestants/vasoconstrictors, cyclosporine, tacrolimus, interferon alpha, mitomycin, etc.) at least three months before the study were not considered, with priority given to 100% treatment-naïve patients with no prior ocular treatment. Patients with previous ocular surgeries, use of contact lenses, or prior ocular pathologies such as ocular hypertension-glaucoma, pteryg-

ium, conjunctivochalasis, keratoconus, neurotrophic keratitis, or ocular pemphigoid were excluded. Those who had undergone oral or subcutaneous allergy vaccine treatments at any time, or who were on treatments such as non-steroidal anti-inflammatory drugs, antihistamines, antileukotrienes (montelukast), corticosteroids, tetracyclines or azithromycin, immunosuppressants, or biological drugs (dupilumab, omalizumab) were also excluded. Participants with associated rhinitis and dermatitis, especially allergic, and systemic diseases, including Sjogren's syndrome, bronchial and pulmonary asthma, or any other bronchopathy, were not included. Finally, children under 10 years old were excluded from the study.

2.3. Preliminary Study and Final Clinical Study to Evaluate Tolerance and Side Effects of the Seawater Treatment

A complete preliminary examination was conducted for each patient at the time of inclusion, including general data (age, sex), pathologies and treatments of general diseases with a special focus on allergic manifestations in other areas (asthma, rhinitis, dermatitis), a full slit-lamp examination of the anterior segment of both eyes, tonometry, and retinography. Schirmer test, TBUT, and fluorescein staining were performed to assess secondary corneal involvement accurately. For the TBUT test, a fluorescein strip (Ful-Glo®) was placed in the inferior conjunctiva moistened with saline solution. TBUT was quantified by counting the time of break-up after three consecutive blinks. Illumination was performed using a Topcon lamp with maximum blue light width. Three values were taken, and the mean of the two closest values was calculated. A TBUT of 10 seconds or less was considered pathological. The Schirmer test was performed after instillation of a double aesthetic drop (Colircusi®, Alcon Laboratory, Barcelona, Spain) and placing a strip (Tear strips, Aivimed GmbH, USA) in the outer third of the lower eyelid, allowing natural blinking. Values less than 10 mm at 5 minutes were considered pathological.

2.4. Final Clinical Study to Evaluate Tolerance and Side Effects of the Seawater Treatment

Weekly follow-up calls were made to assess treatment tolerance, requiring the presence of side effects to interrupt treatment and examine the patient with a slit lamp and conjunctival staining.

2.5. Treatment Protocol

All patients received exclusive treatment with isotonic seawater solution (Quinton® Eye Health) 6 times a day for 4 weeks. The solution was applied as a spray a few centimetres from the patient's eye with the eye slightly open.

As in the case of any other type of ocular spray, patients were instructed on the use of the spray. In brief, before applying the ocular spray, patients should thoroughly wash their hands with soap and water to minimize the risk of contamination. One to two sprays should be applied directly over each closed eyelid (or

slightly open eye) —without applying pressure to the eyelids—and position the spray bottle approximately 10 to 15 centimetres away from the face. One to two sprays (1 - 2 seconds/spray) should be applied directly over each eye.

The seawater solution Quinton® (Quinton® Eye Health supplied by Laboratoires Quinton, Alicante, Spain) sourced from an area of the Atlantic Ocean rich in planktonic proliferation (Bay of Biscay, Spanish coast) and it is microfiltered at 0.22 micrometres in a clean and cold room. It is a solution rich in electrolytes and organic nutrients such as Na^{+}, Cl^{-}, Mg^{2+}, K^{+}, Ca^{2+}, Cu^{2+}, Zn^{2+}, Be^{2+}, D-Biotin, Riboflavin, Nicotinamide, Cyanocobalamin, etc. [26]. Spring water is added to achieve isotonicity and salinity similar to human tears. It is estimated that each spray of about 5 seconds release 3.3 mL of the isotonic seawater.

2.6. Biochemical Analysis of Tears, MMP-9 InflammaDry® Test

The InflammaDry test (RPS, Sarasota, Florida, USA) was used to measure levels of MMP-9. InflammaDry can detect levels of MMP-9 greater than 40 ng/mL, providing only a positive or negative reading [6] [8]. Specifically, patients with a negative InflammaDry test in one of the two eyes before the study were excluded. All tear samples and the InflammaDry test data collection were always performed by a single experienced researcher to avoid potential variables in the evaluation of MMP-9 levels. The test was conducted after a 3-hour period from the last treatment application, under standardized room illumination and temperature conditions (between 20˚C and 25˚C). No aesthetic could be applied to the eye for at least 10 minutes before sample collection. The lower eyelid was gently lowered to expose the lower palpebral conjunctiva, relaxing the eyelid every three touches to allow blinking. The sample collection tip was gently applied 6 - 8 times to different points on the lower eyelid conjunctiva and held for an additional 5 seconds on the inferior conjunctival fornix. A swiping motion was not used for sample collection. The sample was placed in the cassette and the tip soaked in buffer for 20 seconds. After resting horizontally for 10 minutes, the window colour was evaluated. A blue line in the window indicated negative MMP-9 levels, while a red line indicated positive levels. In cases of invalid results (no blue or red line) in either eye, the patient continued treatment, and a new InflammaDry test was repeated under the same conditions 2 days later only in the eye with the previous invalid result. If the result was again invalid, the patient was excluded from the study.

2.7. Statistical Analysis

A preliminary study to calculate the required number of patients was conducted using STATISTICA version 8 software (StatSoft Inc., USA). A descriptive analysis of demographic data and clinical characteristics of patients was performed. For statistical comparison of MMP-9 levels before and after treatment, paired matches case-control study was performed. The significance level was set at $p < 0.01$. Data were analysed using OpenEpi epidemiologic and statistical calculator for public health website [27].

3. Results

3.1. Demographic Data of the Studied Population (n = 50)

A total of 538 patients (1076 eyes) diagnosed with allergic conjunctivitis—including SAC, PAC, VKC, and AKC—were initially screened across various centres. Each patient was classified according to conjunctivitis grade. From this group (n = 538 patients), 50 of them were selected for the study based on meeting all criteria for intensity grade I/II/III and bilateral InflammaDry® test positivity. Patients were included in chronological order of identification until the quota of 50 was reached (See Figure 1).

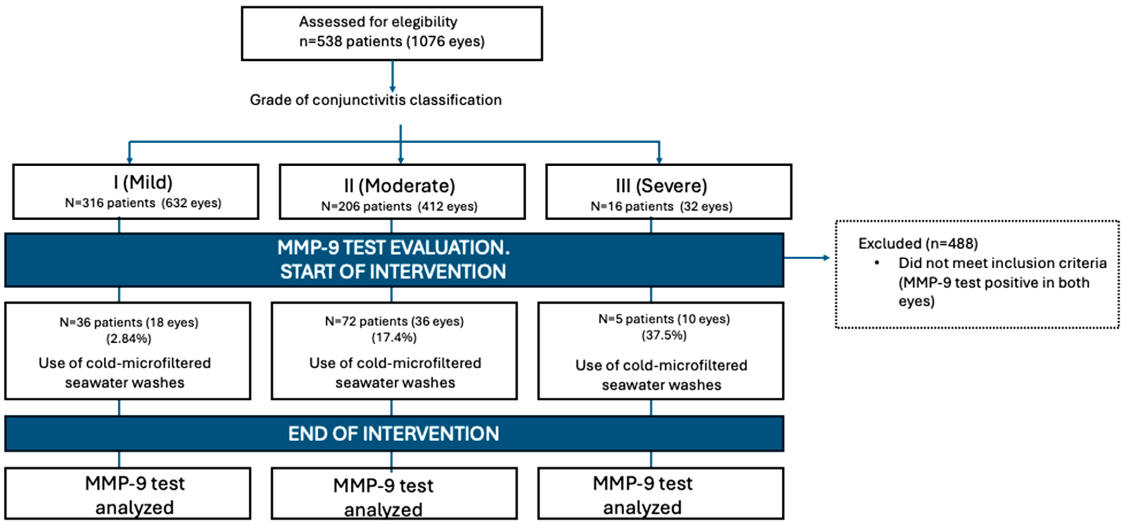

Figure 1. Flow of participants throughout the study.

Regardless of the subtype of conjunctivitis MMP-9 was considered as a good marker of clinical intensity of ocular allergy and for monitoring treatment response. In fact, the higher the severity of the conjunctivitis the higher the percentage of positive test in MMP-9 InflammaDry® test (Figure 1).

Table 2 provides details on gender, age, and type of allergic conjunctivitis of the 50 patients follow up.

Table 2. Demographic Data of patients recruited. Types of conjunctivitis: SAC: acute seasonal allergic conjunctivitis, PAC: perennial-chronic allergic conjunctivitis, VKC: vernal keratoconjunctivitis and AKC: atopic keratoconjunctivitis.

	Data
N	50
Female (%)	28 (56%)
Male (%)	22 (44%)
Age (Mean ± SD)	10 - 75 (27.03 ± 38.19)
Type of allergic conjunctivitis	SAC 18 (36%) PAC 16 (32%) VKC 6 (12%) AKC 10 (20%)

3.2. MMP-9 Positivity and Treatment Response

MMP-9 was evaluated by using the InflammaDry® test at the beginning and at the end of the study 6 times a day for 4 weeks. No side effects or intolerance to the treatment were observed in any patient during the treatment.

Results of InflammaDry® test are show in Figure 2. As it can be observed, the percentage of patients with allergic conjunctivitis who had a bilateral response to seawater treatment, *i.e.*, the rate of test negativity, varied according to the initial conjunctivitis grade: 100% of grade I patients, 89% of grade II patients, and 80% of grade III patients achieved negative MMP-9 levels in tears solely with seawater treatment.

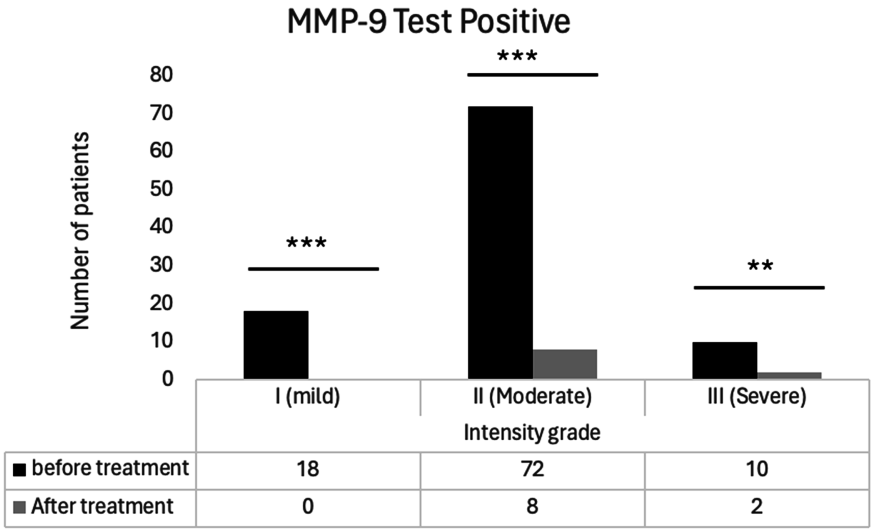

Figure 2. Allergic Conjunctivitis Grade and Treatment Response in terms of MMP-9 negativization (n = 50). MMP-9 was measured by InflammaDry® test. Patients with mild allergic conjunctivitis negativized in 100% of cases, whereas negativization was achieved 89% of patients with allergic conjunctivitis grade II patients, and 80% in the case of grade III allergic conjunctivitis after treatment with Quinton® Eye Health (isotonic seawater). **($p < 0.01$; ***($p < 0.001$).

4. Discussion

Although allergic conjunctivitis can interfere with work, daily activities, and overall quality of life [3] [28], it is estimated that about a third of patients remain undiagnosed and untreated [3]. In addition, the prevalence of allergic conjunctivitis is highly variable in different countries and even in different regions of the same country due to the highly heterogeneous nature of the disease [28] [29]. Nevertheless, with the rising prevalence of allergic diseases, their impact on productivity and healthcare costs is increasing, leading to more research and clinical trials on the subject [1] [3] [28]. While there are now highly effective treatments for acute forms of ocular allergy, managing the chronic, perennial forms remains more challenging and controversial [3].

Treatment focuses on avoiding allergens, relieving symptoms, and preventing

complications [2] [3]. Anticipating exposure to allergens, such as pollen during specific seasons, can help prevent inflammation from becoming chronic and reduce the risk of complications, such as dry eye or the development of more severe forms like atopic keratoconjunctivitis (AKC) [3].

Given the high rates of ocular allergy and the frequency with which these conditions go undiagnosed, there is an urgent need for accessible treatment options. Over-the-counter (OTC) therapies must be designed to meet the specific needs of these patients. Effective OTC treatments can alleviate discomfort by providing symptomatic relief and, ideally, targeting pro-inflammatory factors that contribute to ocular inflammation. By addressing these underlying mechanisms, we can help prevent potential irreversible damage to the eye, enhancing the overall well-being of individuals affected by allergic conjunctivitis.

In a previous study, seawater as monotherapy significantly reduced IgE levels in tears of patients with VKC, achieving negativity in over 60% of cases and reducing the need for corticosteroids and antihistamines to only 17% of cases, with no side effects and excellent tolerance (0% rejection and treatment discontinuation) [23]. This suggests the potential for seawater washes, due to their absence of side effects and excellent tolerance, to become a gold standard and a basic therapeutic step in allergic conjunctivitis, as previously accepted for other allergic systemic diseases like rhinitis and dermatitis [16]-[20].

MMP-9 is a crucial molecule in the pathogenesis, symptom intensity, and chronicity of allergic conjunctivitis, being significantly elevated in the tears of all tested patients with allergic conjunctivitis [7] [30]. In this study, no difference in MMP-9 positivity was observed among the different subtypes of allergic conjunctivitis (SAC, PAC, VKC, AKC); the intensity grade was more important. In grade III allergic conjunctivitis, regardless of the subtype, 37.5% had detectable MMP-9 levels in tears before seawater treatment, compared to 18.4% in grade II and only 2.8% in grade I, establishing MMP-9 as a good marker of clinical intensity of ocular allergy and for monitoring treatment response.

MMP-9 plays a key role in the regulation and repair of the corneal and conjunctival epithelial barrier, inducing a cascade of pro-inflammatory molecules such as interleukin-1, TNF-α**,** NF-kB, platelet-activating factor, AP-1, and TGF-β [31]-[33]. Elevated MMP-9 levels increase corneal epithelial desquamation (keratitis) and secondary ocular irritation (red eye, gritty sensation, etc.). Inhibition of MMP-9 with corticosteroids, cyclosporine, or tetracyclines leads to immediate and significant improvement of the previously inflamed ocular surface [31] [34] [35].

Seawater is a "submerged treasure" yet to be fully explored, with multiple molecules potentially offering therapeutic effects in allergic conjunctivitis and other ocular surface diseases (dry eye, etc.). Among others, marine polysaccharides like chitinase, chitosanase, alginate, agarose, carrageenan, laminaran, etc., with demonstrated anti-inflammatory, neuroprotective, neuroregenerative, and anti-cancer effects have been capable of reducing MMP-9 levels [36]-[39]. Also, phenolic com-

pounds from phytoplankton—sinapic acid, catechin, myricetin, kaempferol, protocatechuic acid, vanillic acid, coumaric acid, ferulic acid, and rutin bromophenol [40]-[42]; and indole alkaloids derived from the marine fungus *Aspergillus versicolor*, such as Asperversiamides, which reduce NO levels by inhibiting iNOS activity with potential benefits for ophthalmic diseases [43] [44]. Also, chaetoglobosin Fex, an alkaloid extracted from the fungus Chaetomium globosum, which can reduce the production of TNF-α, IL-6, and MCP-1 and inhibit IκB-α degradation may be used in diseases related to the eyes [45].

In this study, we explored the potential use of seawater as a treatment in allergic conjunctivitis. Seawater was able to negativize and make MMP-9 levels undetectable in tears of allergic conjunctivitis patients in 89% of cases. This efficacy is similar to that found with other treatments like cyclosporine in allergic conjunctivitis [31]. While part of the efficacy of seawater washes in conjunctivitis may be due to the "washing and dragging" effect of numerous pro-inflammatory molecules and cells (IL-1, IL-6, IL-8, MMP-3, TNF-alpha, macrophages, lymphocytes, NK cells, etc.), previous studies have shown that isotonic saline solution washes without preservatives neither improve nor worsen the ocular surface or tear film in patients with allergic conjunctivitis [46]. Therefore, the high efficacy of frequent seawater washes as monotherapy must be linked more to its mineral composition with lower sodium ion concentration and much higher concentrations of calcium, magnesium, potassium, bicarbonate, copper, and zinc, as well as nutrients like D-biotin, riboflavin, nicotinamide, and cyanocobalamin, and a more alkaline pH (7.9). All these factors reduce the viscosity and volume of mucinous secretions, with anti-inflammatory, anti-apoptotic, antioxidative, and immunomodulatory effects, activating healing and trophic effects on conjunctival and corneal epithelia through the activation of them.

5. Conclusions

This study demonstrated that an isotonic seawater solution significantly reduces the levels of the pro-inflammatory molecule MMP-9 in tears. The product (quinton Eye Health® is applied as a pharmaceutical dosage form already known in the ophthalmology field. It effectively converts positive MMP-9 levels before treatment into 89% negative cases in patients with allergic conjunctivitis. However, some limitations of the study must be highlighted. Despite the good results and excellent tolerance observed in the study, the duration of the clinical trial was short and thus further research should be done in order to ensure the long-term efficacy of such a strategy. Another limitation of the study is the lack of a control (untreated) group in order to compare the benefit of this strategy vs any other potential treatment according to the standard of care.

Although there is an historical use of isotonic seawater for ocular delivery as a medical device from 2019 (Quinton® Eye Health) and previously was considered as a personal care product and commercialized since 2007 (Quinton® Higiene Ocular) without any referred long-term side-effect, a long-term study is required to

ensure the tolerability and safety of seawater washes to evaluate seawater's effectiveness comprehensively and its potential to improve the chronic course of allergic disease.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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