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Chapter 3

Treatments in Infectious and Allergic Conjunctivitis: Is Immunomodulation the Future?

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/52263

1. Introduction

The ocular surface is a functional unit mainly formed by the conjunctival and corneal epithelium (structural component), and tear film (soluble component). Microorganisms and environmental allergens can interact with the tear film, reach the structural component and generate an immune response against them. Understanding the cellular and soluble mediators that are involved in these inflammatory responses not only helps in understanding the mechanisms of current treatments, but also is needed to identification and development of new therapeutics targets. The aim of this review was to investigate the novel and developing therapies, with special emphasis in immunomodulatory drugs/molecules that could have some clinical indication in the treatment of infectious and allergic conjunctivitis in few years.

2. Novel therapies in infectious keratoconjunctivitis

2.1. Interferons (IFN) and adenoviral conjunctivitis

Interferons were first described as the major effector cytokines of the host immune response against viral infections. IFN are well recognized by their potent antiviral properties, however IFN production is also induced in response to bacterial ligands of innate immune receptors and/or bacterial infections, indicating a broader physiological role for these cytokines in host defence and homeostasis than was originally described.

Three main types of cytokines compose the IFN family: type I, type II and type III IFN. Type I IFN family is composed of 16 members, namely 12 IFNα subtypes, IFNβ, IFNε, IFNκ and IFNω. By contrast, the type II IFN family includes only one cytokine: IFNγ, which also exhibits antiviral activities. The third type of IFN is the IFNλ family, which includes IFNλ1 (also known as IL-29), IFNλ2 (also known as IL-28A) and IFNλ3 (also known as IL-28B). On the basis of protein sequence and structure, type III IFN are markedly different from type I and type II IFN and are more similar to members of the interleukin-10 (IL-10) family; however, they provoke antiviral responses and induce the activation of IFN-stimulated genes. [1]

Epidemic keratoconjunctivitis (EKC) is a severe ocular infection, caused by highly contagious adenoviruses Ad8, Ad19, and Ad37. Adenoviral infection of the eye induces keratitis and conjunctivitis, accompanied by pain, lacrimation, red and swollen eye, as well as decreased vision that may last for months or even years. No specific antiviral drugs are currently available for the treatment of EKC or any other infection caused by adenoviruses. Interestingly, it has been suggested that five strains of different serotypes of adenovirus, types 3 (AdV3; species B), 4 (species E), 8, 19a and 37 (species D) involved in acute keratoconjunctivitis are highly inhibited by IFN-b and IFN-g in the A549 cell line, [2] However, IFN therapy in adenoviral keratoconjunctivitis has not been evaluated in clinical trials yet.

2.2. Glycan interactions and EKC

The initial event leading to EKC is binding of the viruses to glycans that contain sialic acid moieties on epithelial cells in the cornea or conjunctiva through trimeric fiber structures extending from the viral particles. The receptor-binding domain is located at the C terminus of each fiber and contains three separate pockets that each can accommodate one sialic acid residue. Ad37 was recently shown to bind to cell-surface glycoproteins carrying a glycan structure named GD1a due to similitude to GD1a ganglioside. The GD1a glycan is a branched hexasaccharide with a terminal sialic acid residue on each of its two arms. Structural studies showed that the two sialic acid moieties dock into two of three sialic acid binding sites in the trimeric knob of the Ad37 fiber protein. Most likely, multiple fiber proteins simultaneously engage several host-cell epitopes containing terminal sialic acids; internalization and subsequent infection follow. In this context, the molecules named ME0322, ME0323, and ME0324 were synthetized as a tri- and tetravalent sialic acid compounds, and interestingly all of theses molecules inhibited the attachment of Ad37 virions to HCE cells in a dose-dependent manner and were at least two orders of magnitude more effective than sialic acid, suggesting a promissory inhibitor of Ad37 infection on corneal cells, composed by a multivalent sialic acid conjugate. If these compounds could be useful as a topical treatment is not known and needs further investigation. [3]

2.3. Vaccines and Herpetic Stromal Keratitis (HSK)

The disease course in herpetic stromal keratitis (HSK) begins with a primary infection by herpes simplex virus (HSV) followed by a period during which the virus enters latency in sensory and autonomic ganglia, after that a reactivation from the trigeminal ganglia follow-

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ing primary infection induce virus transportation to the ocular mucosa via antero-grade movement from the ganglia, ultimately causing herpetic keratitis, conjunctivitis and other ocular sequelae [4]

Many studies have shown that clinical disease is the result of a recruitment of inflammatory cells, mainly polymorphonuclear cells (PMN), macrophages, and T cells to the corneas of patients with HSK. [5] Due to HSK could lead to a potentially blinding disease; several therapeutical strategies are in development to control ocular damage at initial steps of inflammatory process, i.e. vaccination with different HSV epitopes.

Since the early nineties many attempts have been made to develop a vaccine that would be effective in preventing HSK. Most of these vaccines were useful to prevent primary HSK when given prior to HSV infection however failed to prevent recurrent HSK lesions. [6, 7, 8] Recently, a novel construct with a DNA vaccine expressing herpes simplex virus type 1gD and IL-21, appears to be effective in protect from primary lesions, and also ameliorates herpes keratitis severity and time course after corneal infection with HSV-1 in the animal model [9] Nevertheles, future studies are needed in humans HSK to study efficacy of this vaccine.

2.4. Lipids mediators and HSK

Resolvins are lipid mediators that are derived from the v-3 polyunsaturated fatty acids eicosapentaenoic acid and do- cosahexaenoic acid [10] The name of these lipid mediators is related to their main function, control of inflammation. Resolvins are involved in prevention of diapedesis, regulation of dendritic cell costimulatory factors, [11], increased macrophage phagocytosis of apoptotic neutrophils, inhibition of host tissue inflammatory responses, with the release of chemokines and cytokines, [12] promotion of tissue repair, and prevention of host tissue cell death during stress. [13] Interestingly, topical therapy with resolvins in corneas infected with HSV showed a diminished lesion severity and corneal neovascularization when compared with non-treated eyes. Therapy with resolvins, induced a decreased influx of effector CD4+ T cells and neutrophils to corneal tissue; a diminished production of proinflammatory cytokines and molecules involved in ocular neovascularization were also observed during this treatment in the animal model, suggesting resolvins as promissory molecules in the treatment of HSK.

2.5. Dialyzable Leuckocyte Extracts (DLE) and HSK

DLE were described by Lawrence in 1955, who proved that the extract obtained from a dialyzed of viable leukocytes from a health donor presenting a positive percutaneous tuberculin test was able to transfer to a healthy receptor the ability to respond to this test [14] DLE are constituted by a group of numerous molecules all of them with a molecular weight between 1-12 KDa. DLE have been widely used as adjuvant for treating patients with infectious diseases, and deficient cell-mediated immune response. [15]

The most consistent effects of DLE on the immune system are expression of delayed-type hypersensitivity (DTH) and production of cytokines. [16] Despite DLE have been extensively studied in worldwide, in our country, only Transferon® has been approved for human

use by the federal regulatory authorities of health (COFEPRIS), this clarification is relevant, since the following immunological activities correspond exclusively to preclinical and clinical research related to Transferon®. Immunomodulation by Transferon® has been demonstrated by restoration of iNOS expression in a mouse model of tuberculosis, provoking inhibition of bacterial proliferation and significant increase of DTH [17] Transferon® also induces mRNA expression and IFN-γ secretion in peripheral blood mononuclear cells (PBMC) in animals with experimental glioma when compared with non-treated animals. [18] Due to Transferon® induces a Th1 response a clinical study comparing acyclovir treatment and Transferon® during human herpes virus infection was conducted; in that study patients treated with Transferon® had low incidence of clinical complications, better pain control, and also IFN-g was significant increased in serum when compared with patients treated only with acyclovir. [19] Then, our group conducted a second clinical trial to evaluate immunological data and clinical outcome of patients with HSK treated with acyclovir or acyclovir and Transferon® as adjuvant therapy in patients with herpetic keratitis. Interestingly, patients treated with acyclovir and Transferon® showed higher frequency of circulating CD4+IFN-g+ T cells and lower frequency of circulating CD4+IL4+ T cells after treatment; [20], when clinical outcome was evaluated, patients who received acyclovir and Transferon® as adjuvant showed a significant better clinical outcome than patients treated only with Acyclovir after three months of treatment. (Figure 1)

Despite conclusion of this study was that Transferon® could be used as therapeutical tool as adjuvant treatment in herpetic keratitis, additional clinical studies with more number of patients are needed to confirm these results.

2.6. Amniotic membrane as immunomodulator in infectious keratitis

Amniotic membrane (AM) is the inner layer of the fetal membranes that is in contact with the fetus. An avascular stroma and single epithelial cells constitute the amniotic membrane [21] It has been documented in various clinical trials that transplantation of amniotic membrane is therapeutically useful in different superficial ocular pathologies [22, 23, 24, 25] Its beneficial effects for transplantation are due to the following characteristics: amniotic membrane promotes epithelialization, [26] inhibits angiogenesis [27] and has been used as a carrier for ex-vivo expansion of corneal epithelial [28] and endothelial cells [29] Recently, we demonstrated that AM is able to induce apoptosis, inhibit cell proliferation of human PBMC, and abolish the synthesis and the secretion of pro-inflammatory cytokines even when they are LPS stimulated in vitro. [30] Similarly to us, Bauer *et. al.* demonstrated that amniotic membrane transplantation (AMT) in a mouse model of necrotizing HSK, induced an increased rate of local macrophages apoptosis, with decrement in proinflammatory cytokines IL-6, IL-10, IL-12, TNF-α. Nevertheless, in this animal model, the authors suggest that corneas treated with AMT induced peroxisome proliferator-activated receptor-γ (PPAR- γ) which is associated to phenotypical change in macrophages, turning them from classically activated into alternatively activated macrophages or macrophage cell death, through lipid metabolism and PPAR-γ pathway. [31] In the other hand, animal models of *Staphylococcus aureus* keratitis treated with AMT, have suggested that AM improved the healing process,

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resulting in decreased corneal haze and less neovascularization.[32] however the exact molecular mechanism remains unknown and needs investigation. Due to a lack in this molecular aspects clinical use of AM is limited and only in certain cases immunomodulation function of AM could be exploited, i.e. keratitis with secondary ocular surface damage. (Figure 2)

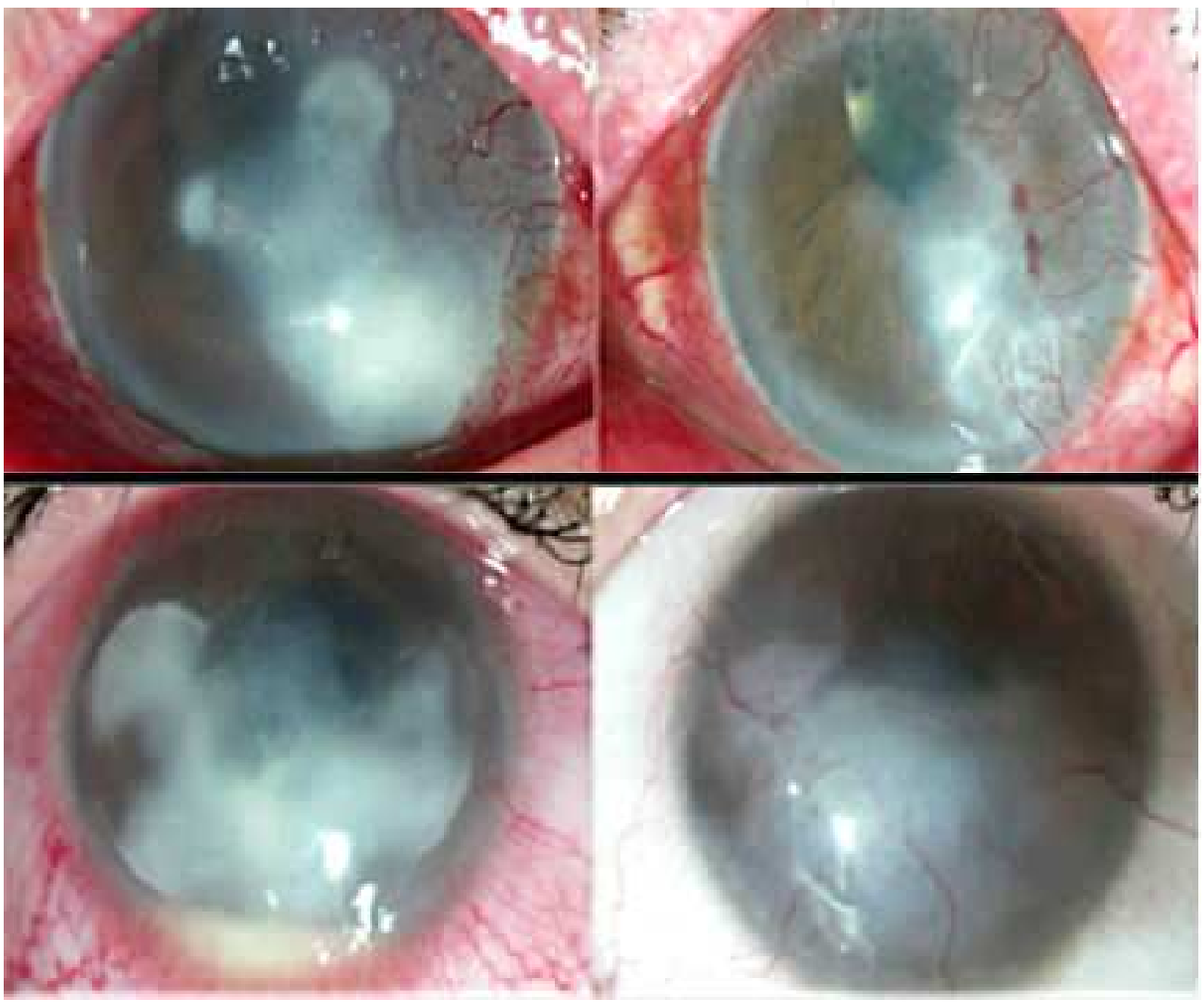

Figure 1. Representative clinical photographs of patients with herpetic keratitis treated with Acyclovir or treated with acyclovir and Transferon®. Upper left, Before treatment; Upper right, Same patient, at 3 months of treatment with acyclovir; Low left, Before treatment; Low right, Same patient, at 3 months of treatment with acyclovir and Transferon®

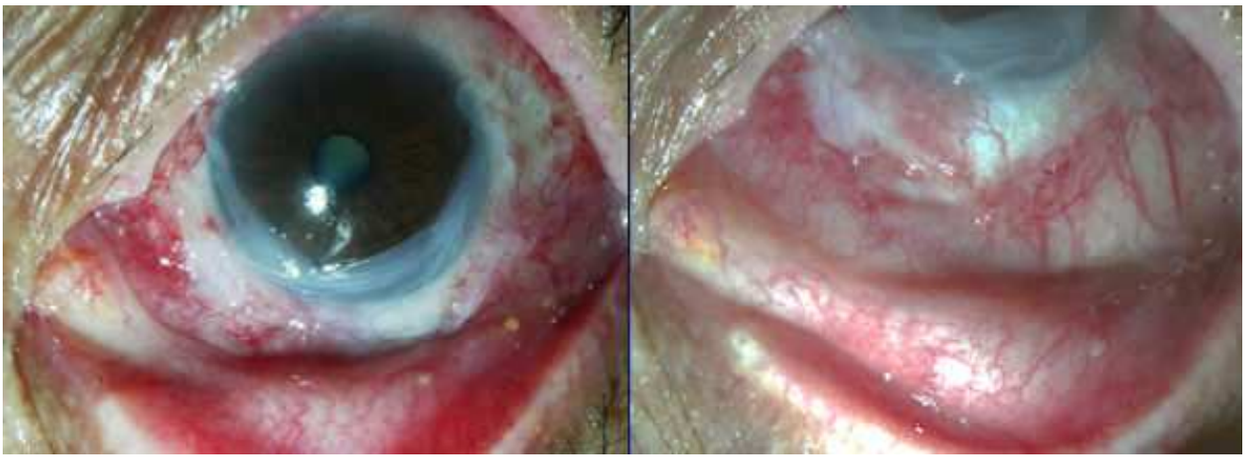

Figure 2. Clinical photographs of AMT in 67 year old female patient with a history of peripheral infectious keratitis secondary to trichiasis. Left, AMT covering the lower peripheral corneal defect. Amniotic membrane was folded several times over the cornea to increase their anti-inflammatory properties. Right, Same patient, 15 days after AMT, clinical photograph showing apparent control of hyperaemia and inflammation

2.7. MIF-CD74 blockade in *Pseudomona aeurginosa* keratitis

Macrophage migration inhibitory factor (MIF) is an integral component of inflammatory responses. MIF induces and sustains expression of several pro-inflammatory cytokines.[33] trough interaction with a receptor complex composed by CD74/CD44 [34] CD74 was first described as class II invariant chain, while CD44 is an adhesion molecule that binds hyaluronic acid and other matrix metalloproteinases. Interaction of MIF with CD74/CD44 results in activation of Mitogen-Activated Protein Kinase (MAPK), production of PGE214 and further induction of inflammatory mediators [35]

Corneal infections by *Pseudomonas aeruginosa* are more difficult to treat and result in worse visual outcome than other bacterial corneal ulcers. Unfortunately the existing therapies fail to control the inflammation secondary to P. aeruginosa keratitis and novel interventions are needed to alleviate tissue damage resulting from local inflammation, recently two studies suggest that blockade of MIF-CD74 ligation ameliorate the disease-associated pathology by decreased proinflammatory mediators and reduced bacterial presence in the cornea [36, 37]

3. Novel therapies in allergic conjunctivitis

Treatment of allergic conjunctivitis can be a challenge by the diverse immunological mechanisms of damage involved in ocular allergic diseases, reviewed in [38]. To date, a wide range of antiallergic drops treatments are available and can be confusing due to lack of improvement at the ocular surface in terms of avoiding anatomical changes in severe cases and control of symptoms in the long time period, reviewed in [39, 40, 41]

Hence our primary goal for treating allergic patients should be preferently to recognize allergy background and ocular inflammation status at the time visit to better establish the

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type and source of antigenic stimuli. In this way, primary action such as avoidance and clearance of antigen with lubrication is recommended preferently in acute but also in the late stage of the chronic forms when dry eye could be implicated. Secondary treatment algorithm includes topical antiallergic agents, which are used towards the reaction characterized by mast cell activation, release of preformed and newly formed mediators such as histamine, prostaglandins, leukotrienes, production of chemokines and expression of adhesion molecules. The aim of treatment in seasonal allergic conjunctivitis and perennial allergic conjunctivitis is directed to symptom relief and control, whereas the objective in the chronic forms of vernal keratoconjunctivitis and atopic keratoconjuctivitis will be also to prevent visual complications or try to identify in early stages possible implication of cornea injury. Therefore the efficacy of therapeutic agents varies from patient to patient in terms of grade of severity at the ocular surface, reviewed in [38] and actual local and systemic status activity of the immune system making the choice of treatment depending on multiple variables, each case must be individualized. In general ocular allergic diseases involve mast cell degranulation that will initiate through inflammatory mediators activation of enzymatic cascades, giving rise to pro-inflammatory mediators and in consequence antihistamines, mast cell stabilizers, non-steroidal anti-inflammatory agents, corticosteroids are agents of common use for acute and chronic conjunctivitis.

Nonetheless this wide range of drugs, management of allergic conjunctivits is still a challenge and immune modulation could be the missing link in the therapeutical approach of ocular allergic diseases.

3.1. Calcineurin inhibitors and atopic keratoconjunctivitis

Calcineurin inhibitors are capable of inducing local immunosuppression more than immunomodulation. Topical [42] and systemic cyclosporine a (CsA) [43] have been suggested in the treatment of severe atopic keratoconjunctivitis. Cyclosporine is effective in controlling ocular allergic inflammation by blocking Th2 lymphocyte proliferation and IL-2 production. It also reduces eosinophils production via inhibition of IL-5 production. Use of CsA appears to be safe and the clinical goal for its use is to eliminate the need/dependence of steroids and favourably alter the long-term prognosis of patients with AKC.

Others calcineurins inhibitors that appears to be well tolerated by patients with severe atopic blepharoconjunctivitis [44] and severe atopic keratoconjunctivitis [45] and acceptable clinical outcome are tacrolimus and pimecrolimus, both of them were used first in atopic dermatitis treatment [46]. To date the real impact of anti-allergic treatment with calcineurin inhibitors is unknown.

3.2. Mapracorat and eosinophils in ocular allergy

Mapracorat is a novel selective glucocorticoid receptor agonist that maintains a beneficial anti-inflammatory activity but seems to be less effective in transactivation, resulting in a lower potential for side effect; it has been proposed for the topical treatment of inflammatory skin disorders. In vitro, Mapracorat inhibited eosinophil migration and IL-8 release from

eosinophils or the release of IL-6, IL-8, CCL5/RANTES, and TNF-α from a human mast cell line with equal potency as dexamethasone, whereas it was clearly less potent than this glucocorticoid in inducing annexin I and CXCR4 expression on the human eosinophil surface; in other hand, animal model of allergic conjunctivitis showed that mapracorat was similar to dexamethasone eye drops in analogous reduction in clinical symptoms of allergic conjunctivitis and conjunctival eosinophil accumulation. [47] The authors suggest this novel glucocorticoid receptor agonist as a candidate to be used in clinical trials of ocular allergy.

3.3. Omalizumab and allergic diseases

Omalizumab is a biological engineered molecule, targeting the Cε3 domain of the IgE molecule. It binds with free IgE and prevents free IgE from attaching to high-affinity IgE receptor (FcεRI) on effector cells such as mast cells, basophils and also on dendritic cells. An IgE-anti-IgE complex is formed, and as a result, free IgE is decreased. [48] Omalizumab has been well studied and used in treatment of asthma [49, 50, 51] and other allergic diseases such as uriticaria and and stational rhinitis [52] Like other immunomodulators mentioned above, clinical trials with allergic conjunctivitis patients are needed to asses the real impact in ocular allergic diseases.

4. Ocular complications with topical or systemic treatments

Allergic reactions to medication could generate ocular manifestations ranging from mild to severe and it would not be considered infrequent. Demonstration of allergy to topical medications could not be easily evaluated by allergen test, but give some information. Direct provocation in conjunctiva with suspicious drug has been reported, [53] the authors of this review do not recommend this method as a diagnostic protocol, however this test could be used as a research tool to investigate immune responses during allergy to topical medication. To evaluate ocular allergy to drug medications, epicutaneous allergen test and immediate-reading intradermal tests are carried out to diagnose immediate hypersensitivity reactions, while atopy patch tests are usually performed to evaluate delayed reactions, reviewed in [38, 54] with this diagnostic methodology, Wijnmaalen et al reported that the most frequent medication-associated allergies were directed against tobramycin, neomycin sulphate and thimerosal. [55]

Mild to severe ocular reactions to drug-medications are also associated with systemic medications (Figure 3) and in some extreme cases could be life threatening or lead to blinding disease such Stevens Johnson syndrome. If Systemic reactions to medications are mediated by IgE hypersensitivity, it could be easy evaluated by flow cytometry with the Basophil Activation Test. (Figure 4)

Principle of this test is simple, basophils are activated in vitro by suspicious medication, if basophils are sensitized to the drug, basophils became active and up regulate on its surface a molecule named CD63. [56] CD63 is an intracellular lysosomal protein whose surface expression is up regulated also on activated platelets, degranulated neutrophils, monocytes,

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macrophages, and endothelium. To be sure that CD63 expressing cells are basophils, analysed cells are also labelled against CD123 and HLA-DR. CD123 is the IL-3Rα, the granulocytic line, including basophils, express constitutively this cluster of differentiation; [57] while HLA-DR is expressed on B lymphocytes, monocytes, macrophages, activated T lymphocytes, activated natural killer (NK) lymphocytes, but is absent in Basophils. Altogether means that by flow cytometry basophils would be CD123+HLA-DR- and only if they were activated by IgE-allergen or drug-medication basophils would be CD63+ [58] (Figure 4).

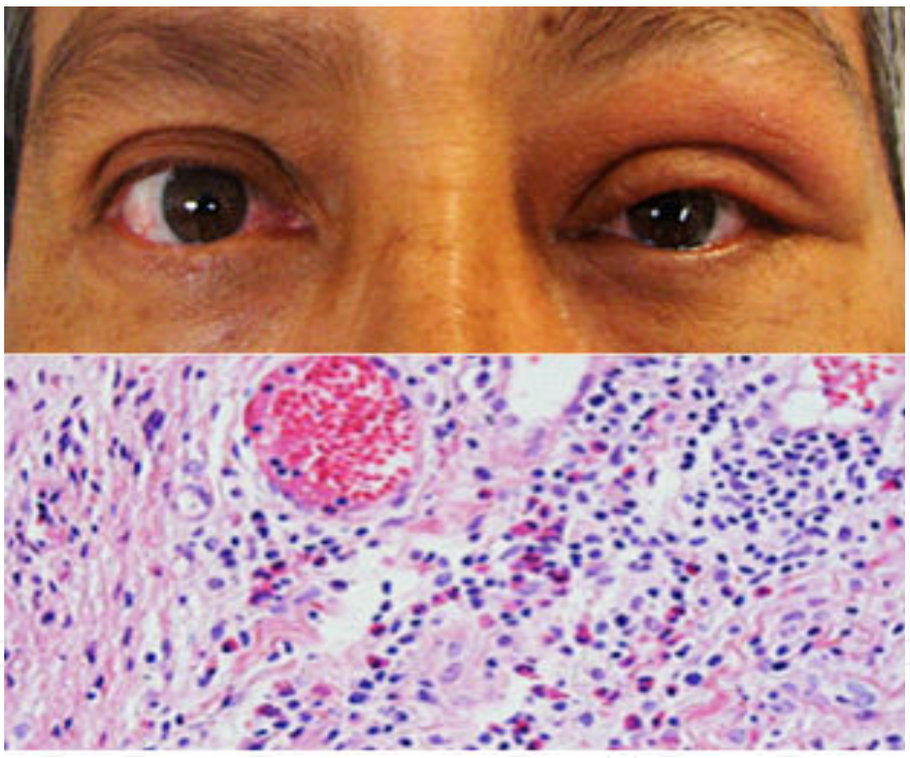

Figure 3. Clinical photograph of a patient with ocular reaction against systemic steroids. Excisional biopsy revealed an extensive eosinophilic infiltrate remaining angiocentric eosinophilic fibrosis. Demonstration of drug allergy was performed by flow cytometry.

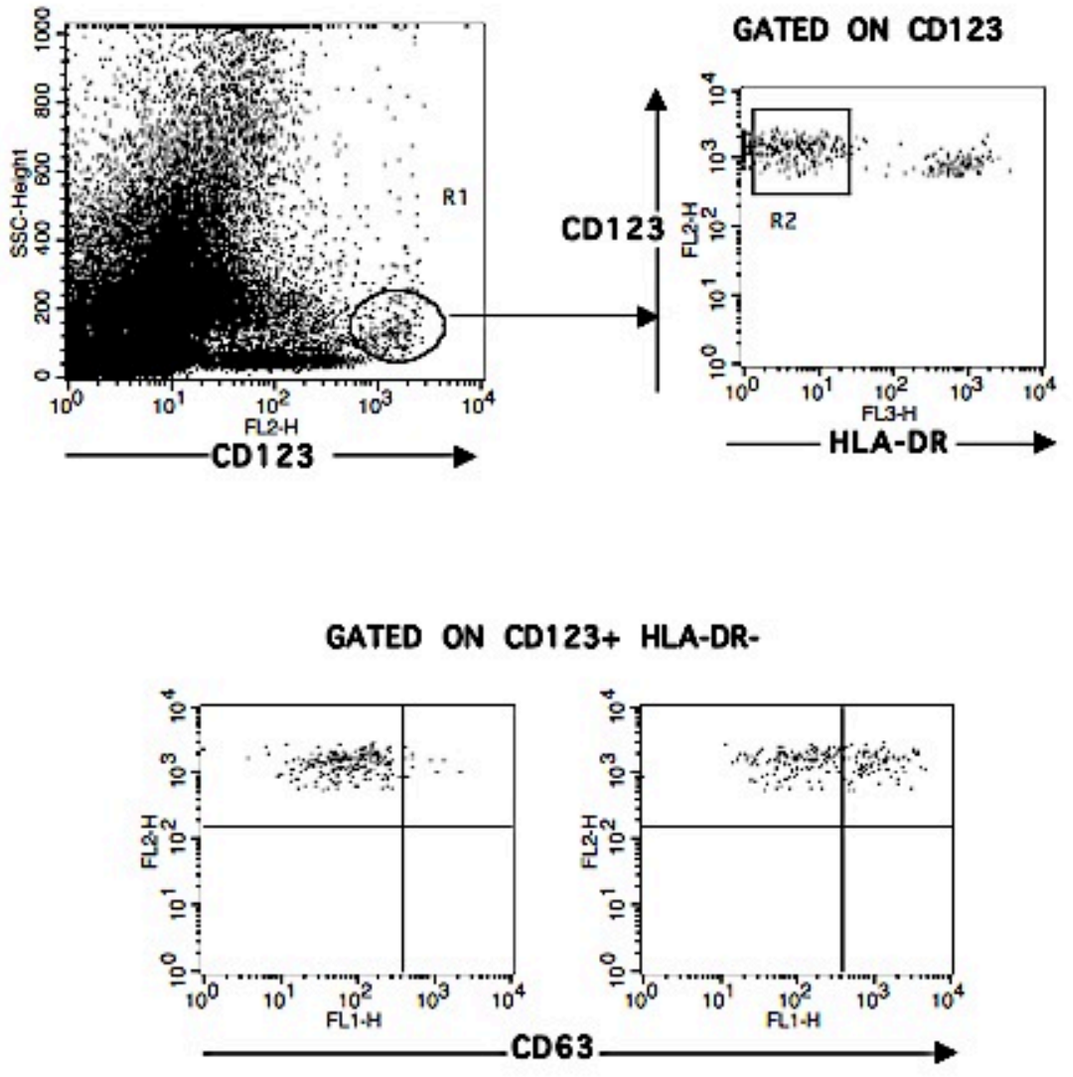

Figure 4. Representative cytometer data of Basophil activation test. Analysis gates are shown at upper dot plots. Upper left, a gate was drawn on CD123 positive cells according to SSC characteristics; these cells correspond mainly to basophils. Upper right, A second gate is performed on HLA-DR negative cells; Dot plots of gated CD123+HLA-DR- cells (basophils) are displayed. Low left, negative test; Low right, Positive test, markedly up regulated expression of CD63 is observed.

5. Conclusions

As the prevalence of allergic disease increases around the world, resistance to antibiotics/antivirals/or antimicotic drugs grows, and virulence of microorganisms improves its capacity of infection, it is clear that more effective therapies and disease-modifying agents are needed. Only treatment evolution will be obtained understanding immune pathophysiological mechanism underlying infectious and allergic diseases. The authors of this review are

http://dx.doi.org/10.5772/52263

convinced that immunomodulation is part of our future as health professionals and are working today to make it posible as soon as posible.

Acknowledgments

C Santacruz and SM Perez-Tapia should be considerer as a first authors indistinctly. This work was supported in part by "Fundación Conde de Valenciana" and Transfer Factor Project.

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