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Potential Therapeutic Approach for the Hormonal Treatment of Lacrimal Gland Dysfunction in Sjögren's Syndrome

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Ocular Impact, Prevalence, Etiology, and Current Therapy of Sjögren's Syndrome

The preocular tear film serves an indispensable role in the preservation of corneal integrity, the defense against viral and bacterial challenge, and the maintenance of visual acuity (1). These functions, in turn, are inextricably linked to the stability, tonicity, and/or composition of the tear film structure, which includes an underlying mucin foundation, a substantial, middle aqueous component, and an overlying lipid layer (1, 2). Disruption, deficiency, or absence of the tear film may lead to intractable desiccation of the corneal and conjunctival epithelium, ulceration and perforation of the cornea, an enhanced incidence of infectious disease, and, ultimately, pronounced visual disability and blindness (2, 3).

Throughout the world, countless individuals suffer from tear film dysfunctions, which are collectively diagnosed as keratoconjunctivitis sicca (KCS) or, simply, dry eye (1, 2). These lacrimal abnormalities may be subdivided into four general categories: *aqueous tear deficiencies,* which are most frequently responsible for dry eye states, originate from lacrimal gland disorders and include autoimmune disease, congenital alacrima, paralytic hyposecretion, or excretory duct obstruction; *mucin deficiency,* which is observed in various conjunctival cicatrization conditions, such as Stevens–Johnson syndrome, trachoma, pemphigoid, thermal and chemical burns, as well as hypovitaminosis A; *lipid abnormalities,* which may occur during eyelid inflammation (e.g., chronic blepharitis); and *diminished eyelid function* (1). To clinically manage dry eye states, the principal therapy is exogenous replacement with tear substitutes (3–5). Thus, approximately 7 to 10 million Americans currently require the use of artificial tear preparations (6).

The greatest single cause of KCS worldwide, excluding those countries wherein *Chlamydia trachomatis* infections remain prevalent, is Sjögren's syndrome (2). This syndrome is an autoimmune disease that is present almost exclusively in females and is accompanied by a pronounced and progressive lymphocytic infiltration into the perivascular and periductal areas of main and accessory lacrimal glands, an immune-related, extensive destruction of acinar and ductal tissues, and KCS (7–10). In primary Sjögren's syndrome, which occurs in about 50% of the patient population, the disease may also be associated with an immunological disruption of the salivary gland and pronounced xerostomia. In secondary Sjögren's, the disorder is accompanied by another disease, which is most often rheumatoid arthritis and less frequently systemic lupus erythematosus, scleroderma, polymyositis, polyarteritis nodosa, Hashimoto's thyroiditis, chronic hepatobiliary disease, chronic pulmonary fibrosis, purpura hyperglobulinemia, or Raynaud's phenomenon (2, 11). During the course of Sjögren's syndrome, autoimmune sequelae may also encompass focal lymphocytic adenitis of eccrine and mucosal glands, biliary cirrhosis, sclerosing cholangitis, pancreatitis, atrophic gastritis, interstitial nephritis and pneumonitis, peripheral vasculitis, B cell lymphoma, and a diverse array of central and peripheral nervous system and skeletal muscle complications (12, 13).

Sjögren's syndrome is the second most common autoimmune disease in the world, with an estimated prevalence of 0.5 to 1.0% (7, 14). Although the absolute incidence is unknown, one expert's impression is that Sjögren's syndrome may outrank rheumatoid arthritis, which afflicts 2 to 5% of the adult population over 55 years of age (13). Another estimate projects that a minimum of 3.2 million Americans may suffer from this autoimmune disorder (6).

The etiology of Sjögren's syndrome may be due to the interaction of numerous factors, including those of genetic, endocrine, neural, viral, and environmental origin (15, 16). However, a potential cause may relate to primary infection by, and reactivation of, Epstein–Barr virus (EBV) and/or cytomegalovirus (CMV) (17–20). These herpes viruses are present in lacrimal and salivary glands of Sjögren's patients (17–20) and may induce the inappropriate HLA-DR expression, T helper/inducer cell activation, B cell hyperactivity, and autoantibody production evident in these affected tis-

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sues (8). However, whether herpes, or even retroviral (21, 22), action represents a cause of, or merely an epiphenomenon in, Sjögren's syndrome remains to be determined (23–25).

According to one patient, "Sjögren's is misery" (9). According to certain physicians, a perception is that ocular manifestations of Sjögren's syndrome may be clinically irreversible (7), an eye disease to be controlled, yet not cured (10). In the scientific literature, reports suggest that systemic or topical administration of estrogens (4), cyclosporine A (6), or glucocorticoids (26) might alleviate the disorder. However, additional studies indicate that such pharmaceutical exposures are ineffective (27–29) (E. H. Sato and D. A. Sullivan, manuscript in preparation), and, in fact, may accelerate and/or amplify the disease (28, 30). Indeed, estrogen action may be involved in the etiology of Sjögren's syndrome (30, 31). Other investigators have proposed that tear stimulants, such as bromhexine (32) or isobutylmethylxanthine (33), might improve ocular symptoms. These drug effects, though, may be subjective (34), susceptible to tachyphylaxis (4), and/or limited by the requirement for functional and responsive lacrimal tissue (4, 35). Therefore, the currently prescribed, therapeutic approach for the treatment of ocular manifestations in Sjögren's syndrome is the frequent application of artificial tear substitutes, which permit lubrication of the eye's anterior surface (3, 4, 5, 9, 10). Unfortunately, this therapy does not ameliorate the inherent, ocular immunopathology and does not assuage the psychological trauma associated with a chronic, extremely uncomfortable, and vision-threatening disease (3).

Androgen Influence on Lacrimal Autoimmune Expression in Sjögren's Syndrome

Autoimmune disorders commonly display a sexual dichotomy, with estrogens increasing disease severity in females and androgens suppressing autoimmune sequelae in males (15, 16, 36–38). In fact, androgen therapy has been utilized to effectively diminish autoimmune expression in animal models of systemic lupus erythematosus (SLE), thyroiditis, polyarthritis, and myasthenia gravis (15, 38–43), as well as the human condition of idiopathic thrombocytopenic purpura (44). Therefore, androgen treatment might also provide a potential therapy for the immune-associated, lacrimal gland defects in Sjögren's syndrome.

In support of this hypothesis, a number of observations demonstrate that androgens exert a significant, regulatory impact on the structure, function, and immune expression of lacrimal tissue in both health and disease. First, androgen action appears to account for many distinct, gender-related differences in the morphology, histochemistry, biochemistry, molecular biology, and immunology of the lacrimal gland, in a variety of species, including mice, rats, hamsters, guinea pigs, rabbits, and humans (45). These gender-associated variations encompass differences in the area, shape, membrane characteristics, vesicle quantity, and nuclear appearance of acinar cells, the content of DNA, total RNA, and specific mRNA, the density of specific lymphocytes, and/or the level of immunoglobulins, enzymes, hormone responsiveness and binding sites, adrenergic receptors, glycoproteins, and collagen (45, 46). When investigated, these dimorphic variations have typically been attributed to androgen, but not estrogen or progestin, influence (46). In fact, female sex steroids do not appear to play a meaningful role in lacrimal dynamics (45, 47, 48) (D. A. Sullivan *et al.*, manuscript in preparation).

Second, androgens regulate the lacrimal gland's secretory immune system (45), which is designed to protect the ocular surface against bacterial colonization, viral attachment, parasitic infestation, and fungal- or toxin-induced impairment (49). This endocrine control, which has been characterized in experimental animals, is unique to the eye and involves modulation of the synthesis and secretion of IgA and secretory component (SC), the IgA antibody receptor (50–55). Of interest, androgen regulation of lacrimal immunity may be significantly augmented or curtailed by other hormones (e.g., insulin, factors from the hypothalamic–pituitary axis), neural agents (e.g., vasoactive intestinal peptide, autonomic analogues), lymphokines (e.g., interleukin-1, tumor necrosis factor-α), and autocoids (e.g., prostaglandin E_2) (54, 56–59).

Third, systemic androgen administration to animals (60, 61) or humans (62–64) after the onset of Sjögren's syndrome may result in a significant amelioration of autoimmune sequelae in the lacrimal gland, and/or an apparent reduction in ocular symptoms. Relevant animal research has utilized mouse models [MRL/Mp-lpr/lpr (MRL/lpr) and NZB/NZW F1 (F1) females] of Sjögren's syndrome; lacrimal tissues of these animals are analogous to those of humans and contain extensive, multifocal, and confluent lymphocytic infiltrates in perivascular and periductal regions, and marked glandular disruption (65–67). These murine investigations have demonstrated that:

(a) Testosterone therapy induces a precipitous decrease in the extent of lymphocyte infiltration in lacrimal tissue. This hormone action, which is observed after either physiological or supraphysiological androgen treatment, involves significant abrogations in both infiltrate size and number. Moreover, examination of lacrimal tissue of testosterone-treated mice shows almost no evidence of acinar or ductal cell destruction (60, 61).

(b) Androgen exposure exerts both a quantitative and a qualitative influence on inflammatory cell populations in the lacrimal gland of MRL/lpr mice. Thus, testosterone treatment dramatically decreases the to-

tal number of T cells, helper T cells, suppressor/cytotoxic T cells, Ia-positive lymphocytes, and B cells. Androgen administration also significantly diminishes the lacrimal density, as well as the frequency, of $B220^+$ cells, which may be responsible for the striking peripheral lymphadenopathy in MRL/lpr mice (107).

(c) Testosterone's suppression of focal infiltrate area, number of inflammatory cell foci, and percentage lymphocyte infiltration in lacrimal tissue may be duplicated by therapy with 19-nortestosterone and cyclophosphamide, but not by treatment with estradiol, danazol, cyclosporine A, or dexamethasone. Androgen exposure also reduces lymphocyte infiltration in salivary glands, but not in peripheral or mucosal lymph nodes (E. H. Sato and D. A. Sullivan, manuscript in preparation).

(d) Androgen action is paralleled by an increase in the lacrimal gland output of IgA antibodies (D. A. Sullivan *et al.*, manuscript in preparation), the secretion of which may be diminished in mucosal sites in Sjögren's syndrome (68).

As concerns humans, three uncontrolled, clinical studies, which involved the systemic androgen treatment of patients with Sjögren's syndrome, demonstrated a hormone-related decrease in ocular signs and symptoms (62–64) and an apparent 4- to 10-fold rise in tear flow (64). These findings were of particular interest, in that male and female patients with SLE, who may also suffer from secondary Sjögren's syndrome, have reduced serum levels of androgens (69, 70). However, these therapeutic effects following hormone administration were not observed in two additional studies (71, 72), although data in one of these investigations indicated that androgen exposure stimulated a 104% increase in mean tear volumes (Schirmer's score), compared to pretreatment values (72). Whether variations in the structure, route of administration or concentration of androgenic compounds, treatment schedules, and/or hormone metabolic rates account for these differential results remains to be clarified.

Overall, these combined findings show that androgens may suppress autoimmune expression in lacrimal glands of animal models, and possibly patients, with Sjögren's syndrome. To our knowledge, no other hormone or pharmaceutical agent, with the exception of cyclophosphamide (E. H. Sato and D. A. Sullivan, manuscript in preparation), has this effect. This androgen action may represent a tissue-specific response, because endocrine-immune interactions frequently appear to be site-specific and dependent upon the local microenvironment (45). Thus, androgens depress autoimmune sequelae and stimulate secretory immune function in lacrimal glands, but do not influence these parameters in distant peripheral lymphoid or mucosal tissues (45, 53, 60, 61) (E. H. Sato and D. A. Sullivan, manuscript in preparation). Moreover, androgen therapy does not correct various systemic immune abnormalities in MRL/lpr mice (73, 74) (E. H. Sato and D. A. Sullivan, manuscript in publication). It is true that testosterone inhibits autoimmune inflammation in salivary glands of murine models of Sjögren's syndrome, but the nature of this hormonal influence may be unlike that found in lacrimal tissue. The magnitude of lymphocytic infiltration in salivary tissue is less extensive (60, 65) (E. H. Sato and D. A. Sullivan, manuscript in preparation) and the inherent immune cell susceptibility to androgens and other pharmaceuticals is quite different (60) (E. H. Sato and D. A. Sullivan, manuscript in preparation) than that found in lacrimal glands. Furthermore, androgen target cells in salivary [e.g., granulated convoluted tubule cells (75)] and lacrimal [e.g., acinar (55)] tissues, as well as focal lymphocytic profiles in these glands (20, 76–78), (E. H. Sato *et al.*, submitted for publication) are dissimilar. As an additional consideration, the underlying nature, pathogenesis, and/or development of autoimmune disease in the lacrimal gland may be somewhat unique. Consistent with this hypothesis is the observation that cyclophosphamide reverses autoimmune expression in lacrimal tissue (E. H. Sato and D. A. Sullivan, manuscript in preparation), but has no effect on pulmonary perivascular inflammation (79), in female MRL/lpr mice. In addition, therapy with glucocorticoids (E. H. Sato and D. A. Sullivan, manuscript in preparation), danazol (80), or cyclosporine A (81) may correct certain systemic or salivary immune dysfunctions in MRL/lpr mice, but these agents do not ameliorate lacrimal autoimmunity in the MRL/lpr model of Sjögren's syndrome (E. H. Sato and D. A. Sullivan, manuscript in preparation).

Mechanism of Androgen Action on Lacrimal Tissue in Sjögren's Syndrome

Regarding potential mechanisms of androgen action on lacrimal autoimmune expression, several possibilities exist that are not mutually exclusive. First, androgens may act by interfering with the immigration, proliferation, or activity of inflammatory lymphocytes in lacrimal tissue. In support of this explanation, these hormones are known to influence lymphocyte migration, maturation, and function (82–85). However, given the scarcity of androgen receptors in differentiated lymphocytes (86, 87) and the absence of hormonal impact on peripheral lymphadenopathy in MRL/lpr mice (73) (E. H. Sato and D. A. Sullivan, manuscript in preparation), it is unlikely that androgens exert direct effects on these cells. Second, testosterone could downregulate Ia expression on lacrimal parenchymal cells, considering that presentation of this class II antigen is enhanced in many exocrine tissues during autoimmune disease (77) and may be susceptible to androgen control (15). Yet, this potential explanation is also improbable: lacrimal glands of MRL/lpr mice do not ap-

pear to express detectable Ia antigens on epithelial cells distant from focal infiltrates (107). Furthermore, cyclosporine A (88) and dexamethasone (89) have been shown to reduce Ia expression in various tissues, but have no apparent effect on lymphocyte infiltration in MRL/lpr lacrimal glands (E. H. Sato and D. A. Sullivan, manuscript in publication).

Third, androgens might indirectly control lacrimal autoimmunity by first interacting with target organs such as the thymus, which plays a critical role in autoimmune phenomena (73), or the hypothalamic–pituitary axis, which may regulate androgen immunoactivity in lacrimal tissue (54–57). However, an androgen–thymic pathway would not appear to explain the uniform androgen, but opposing thymic, effects on autoimmunity in MRL/lpr and F1 mice (73). In addition, hypothalamic–pituitary involvement would most likely elicit a far greater spectrum of immune alterations than direct androgen effects alone, given this axis' tremendous regulatory impact on systemic and mucosal immunological processes (45, 90, 91). Fourth, androgens may act through local epithelial cell receptors to stimulate cytokine production and thereby indirectly modulate the accumulation, proliferation, and/or activity of inflammatory lymphocytes in lacrimal tissue. In this regard, androgens have been shown to (a) associate with specific, high-affinity receptors in lacrimal tissue of male and female animals (92) (D. A. Sullivan *et al.*, manuscript in preparation); (b) directly regulate lacrimal epithelial (acinar) cell function (55, 58, 59); and (c) control the epithelial cell secretion of cytokines that may modulate lymphocyte dynamics (93). It is possible that such hormone-induced, anti-inflammatory cytokines might nonspecifically suppress lymphocyte foci in lacrimal tissue, which appears to be the principal consequence of androgen exposure in MRL/lpr mice (107). One putative cytokine for the mediation of androgen action could be SC, which is synthesized and secreted by acinar cells and controlled by androgenic hormones (45, 55, 58, 59). Although this glycoprotein is primarily associated with IgA transport (45, 94), free SC has recently been demonstrated to inhibit phospholipase A_2 activity and prevent arachidonic acid release (95). Therefore, given that lymphocytic infiltration both compresses glandular lumina and disrupts acinar cells, androgen-induced free SC could be released into lacrimal tissue stroma and possibly serve to uniformly decrease local inflammation. As a corollary to this hormone effect, androgens are also known to stimulate lacrimal IgA production in experimental animals through as yet undefined mechanisms (54). Immunoglobulin A-containing plasma cells are predominant in lacrimal tissue (45) and IgA release and binding to inflammation-related antigens (e.g., viruses in human lacrimal glands) could theoretically enhance phagocytosis and antibody-mediated cellular cytotoxicity through Fc association with polymorphonuclear leukocytes, macrophages, T cells, and natural killer cells (96, 97). However, whether IgA antibodies play a protective role within lacrimal tissue during Sjögren's syndrome has yet to be clarified.

Potential Therapeutic Approaches for the Treatment of Lacrimal Gland Disorders and KCS in Human Sjögren's Syndrome

Given the preceding review, three therapeutic approaches, which require further experimental analysis, may provide a potential treatment for lacrimal gland disorders and KCS in human Sjögren's syndrome. These strategies, which are based upon the recognition that the endocrine, neural, and immune systems interact through extensive, regulatory pathways (90, 98–101), are:

(a) Administration of testosterone analogues with attenuated virilizing properties may directly suppress lacrimal gland immunopathology, thereby inhibiting immune-mediated destruction of acinar and ductal cells and alleviating the infiltrate-induced compression of glandular ducts. This hormone action might then permit the secretion of at least basal tear volumes, as well as make available regions of functional lacrimal tissue that may respond to exogenous tear stimulants; it is estimated that a tear secretion rate of only 0.1 μl/min could maintain a normal tear film under favorable conditions (1). Our laboratory is currently evaluating a diverse array of androgenic compounds in order to identify an optimal hormone for the potential treatment of autoimmune symptoms in lacrimal tissue of Sjögren's patients. These studies are being performed with the understanding that multiple parameters, including the concentration, route of application, pharmacokinetics, and potential toxicity of hormonal substances, are critically important in the selection of safe and effective compounds for immune intervention.

(b) Considering that the androgen-induced suppression of lacrimal immunopathological lesions may be mediated through site-specific cytokines, the identification, isolation, and administration of such factors may constitute a possible approach for future ocular treatment in Sjögren's syndrome. In this regard, the recent development of optimal, serum-free, culture conditions for the maintenance of hormone-responsive acinar cells (59, 102) may facilitate research to establish the existence of, and to identify, putative epithelial mediators. However, because androgen action on lacrimal tissue may also be modulated by a variety of secretagogues (e.g., cAMP stimulators), neural transmitters from peptidergic, sympathetic, and parasympathetic pathways, autocoids, and lymphokines (58, 103), the precise isolation of endocrine-related factors might be exceedingly complex.

(c) Topical inoculation of anti-viral compounds may

be effective in counteracting the viral (e.g., EBV and/or CMV)-induced infection in lacrimal tissue that researchers postulate may precipitate the gland's immune-associated dysfunction (17, 19, 20). This approach, at present, is highly speculative: current scientific information does not definitively show that these viruses are directly involved in the pathogenesis or progression of Sjögren's syndrome (23–25). To test this hypothesis, our laboratory is presently evaluating animal models of virus-related lacrimal gland infection. These studies include utilization of specific herpes and corona viruses that are epitheliotropic and, from literature sources, are known to elicit a distinct, periductular infiltration of lymphocytes in the lacrimal gland, significant interstitial edema, widespread necrosis of the acinar and ductal epithelium, degenerative and atrophic alterations in acinar cells, diminished tear flow, and/or keratoconjunctivitis sicca. Such research may permit assessment of the role of acute viral infection or viral reactivation in lacrimal gland inflammation. Moreover, given that viral infections may well be susceptible to endocrine or neural influences (104–106), studies designed to determine the impact of hormones, neuropeptides, or cytokines on viral activity both *in vivo* and *in vitro* may allow the identification of appropriate pharmaceuticals for anti-viral treatment.

In summary, Sjögren's syndrome is a multidimensional, autoimmune disorder that may significantly compromise lacrimal gland function, corneal integrity, and visual acuity. However, research designed to advance our understanding of the endocrine and neural regulation of the immune system in specific ocular tissues may lead to the development of a safe and effective therapy to cure this disease.

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