Nava-Castañeda A et al
Interferon α-2b for Ocular Surface Squamous Neoplasia
Nepal J Ophthalmol 2018; Vol 10 (20): 143-150
DOI: https://doi.org/10.3126/nepjoph.v10i2.18574

Original Article

Management of Ocular Surface Squamous Neoplasia with Topical and Intralesional Interferon Alpha 2B in Mexicans

Ángel Nava-Castañeda[1], Joaquín Hernández-Orgaz[1], Lilia Garnica-Hayashi[1], Alberto Ansart[1], Gonzalo Matus[1], José L. Tovilla-Canales[1], Francisca Zuazo[1]
[1]Instituto de Oftalmología Fundación de Asistencia Privada Conde de Valenciana

Abstract

Introduction: Ocular surface squamous neoplasia (OSSN) is the most common non-pigmented ocular surface neoplasm and it can originate from the conjunctiva and/or corneal epithelium. Since the rate of recurrence after surgical excision is high, chemotherapeutic and immunotherapeutic agents such as interferon alpha-2b (IFN α-2b) have been used for its treatment. **Objective:** Our objective is to describe the demographic variables of patients with OSSN treated with IFN α-2b and to describe the outcomes of its use in Mexican patients, treated between 2011 and 2017 at Instituto de Oftalmología Fundación Conde de Valenciana. **Materials and Methods:** This is a non-randomized retrospective interventional case series. We reviewed the files of patients older than 18 years, with clinical and/or histopathological diagnosis of OSSN, treated with IFN α-2b alone or in combination with surgery, with a minimum of 6 months follow-up. We studied demographic variables, such as gender, age, eye affected and associated risks factors; we also studied the type of therapy with interferon (topical, intralesional and/or associated with surgery), time of treatment, time of follow up, recurrences and complications. **Results:** A total of 39 patients were included. The mean age of diagnosis was 61 ± 16 years and OSSN was more frequent in males (64.1% of cases). Most of the cases (43.6%) had no identifiable risk factors. The mean time of IFN α-2b treatment was 5 ± 2 months, being higher in the intralesional group (6.5 months) than in the topical group (4.2 months). The clinical resolution with the use of IFN α-2b was evidenced between 0.5 and 10 months, being achieved in 87.1% of the patients. **Conclusions:** The use of IFN α-2b is effective for the treatment of OSSN with a high success rate (87.1%) and a low incidence of relapse (5 cases), with no reported complications during follow up.

Key words: Ocular surface squamous neoplasia; Interferon alpha 2b; chemotherapeutic agents, immunotherapeutic agents.

Conflicts of Interest: Nil
Financial Interest: Nil
Received: 30/02/18 Accepted: 29/05/18

Corresponding author
Ángel Nava-Castañeda, MD, PhD
Address: Chimalpopoca #14 Colonia Obrera, México DF. CP 06800
Telephone: 52 + 5554421700
E-mail: angellusnc@hotmail.com

Introduction

Ocular surface squamous neoplasia (OSSN) is the most common non-pigmented ocular surface neoplasm (Shields et al, 2004), originating from the corneal and/or conjunctival epithelium. The term ocular surface squamous

neoplasia was proposed by Lee and Hirst (Lee and Hirst, 1995), which includes dysplastic and carcinomatous lesions of the ocular surface. These can affect the entire thickness of the epithelium (carcinoma in situ) or cross the basement membrane and invade the stroma. Genetic factors, Ultraviolet B radiation, human papillomavirus (HPV) 16 and 18, human immunodeficiency virus (HIV) (Mata et al., 2014), intense smoking and exposure to petroleum products (Scott, Karp and Nuovo, 2002; Karp et al., 2010) have been associated with its etiology.

There are different forms of treatment currently reported in the literature, but surgical excision with a "no touch" technique is the most accepted (Fraunfelder and Wingfield, 1980). However, the rate of recurrence with this technique remains high, reported from 33% with negative surgical borders and up to 56% with positive surgical margins. (Tabin et al, 1997) Because of this, some adjuvant agents were introduced. Among these adjuvants are chemotherapeutic agents such as mitomycin C and 5-fluorouracil, antiviral agents such as cidofovir, and immunotherapy agents such as interferon alpha-2b (Poothullil and Colby, 2006). These present a non-invasive method to treat the conjunctiva, achieving a high concentration, with minimal adverse effects, that can be maintained or suspended according to the clinical response (de la Cruz et al., 2014), trying to avoid the potential stem cells deficiency associated with an extensive surgical resection (Karp et al., 2010).

Interferon alpha-2b (IFN α-2b) is a glycoprotein produced by leukocytes (Karp et al., 2010) against viral infections (Fernandes et al., 2014). It has antiviral, antimicrobial and antineoplastic activity; the latter due to the combination of antiproliferative, antiangiogenic and cytotoxic effects (Bracarda, Eggermont and Samuelsson, 2010). IFN α-2b antitumor effect is achieved by a direct and indirect mechanism. It has a cytostatic effect that increases the length of cell cycle time in malignant cells and depletes essential metabolites, slowing tumor growth. It also inhibits biosynthetic enzymes, stimulates apoptosis and the induction of antibodies against tumor cells, the expression of cell surface antigens; and tumor cytotoxicity through immune response (Karp et al., 2010; Fernandes et al., 2014).

IFN α-2b has less adverse effects than mitomycin C (de la Cruz et al., 2014) and also better tolerance (Karp et al., 2010). It is used for the treatment of ocular malignant tumors, topically as well as via perilesional or subconjunctival injection routes (Maskin, 1994).

The objective of this article is to describe the demographic variables of patients with OSSN treated with IFN α-2b and describe the results achieved in our patients.

Material and Methods

Study design: non-randomized retrospective interventional case series.

We searched the electronic file of patients with a clinical and/or histopathological diagnosis of ocular surface squamous neoplasia from March 2011 to March 2017. We included patients older than 18 years who gave their informed consent to be treated with IFN α-2b alone or in combination with surgery, which would have a complete file, photographic control and minimum follow-up of 6 months. We studied demographic variables, type of therapy with interferon (topical, intralesional and associated with surgery), time of treatment, time of follow-up, relapse and complications.

Type of therapy

1. Topical: the dose of IFN α-2b was 1 million international units (IU) in 1 ml. Instillation of one drops every 6 hours until 1 month after the clinical resolution of the disease. The follow-up was performed monthly until three months after clinical resolution

of the lesion, then three months thereafter and then bi-annually.

2. Intralesional / subconjunctival: the dose of IFN α-2b was 3 million IU in 0.5 ml, applied once a week until the resolution of the disease. Follow-up was weekly until clinical resolution, and then it was monthly with an eventual taper to every 6 months as described in the topical treatment group.
3. Topical + Surgery: the strength and dosing of IFN α-2b were the same as in the topical group, until tumor immuno-reduction was achieved and then conventional no-touch surgery with wide margins excision (and with the application of absolute alcohol to the corneal epithelium and double row of cryotherapy to the conjunctival margin) was performed. The defect was left uncovered and no sclerectomy was performed. Follow-up was weekly, then monthly for 3 months, three months thereafter and then every 6 months. Topical interferon therapy was continued for three more months after the surgical resection.

Results

A total of 43 OSSN patients, treated with IFN α-2b were found. Four were excluded because the diagnosis was non-specific.

The mean age of the diagnosis was 61±16 years, with a range from 18 to 84 years. OSSN was more frequent in males, presenting in 64.1% of the cases (Table 1 and Chart 1).

The right eye was most frequently affected (53.8% of the cases).

In our series, 53.6% of the cases had confirmed the histopathological diagnosis of OSSN. Of this subset, the most frequent diagnosis was invasive squamous cell carcinoma in 35.8% and carcinoma in situ in 17.8% of the cases. 46.4% of the total cases were diagnosed with OSSN clinically, without biopsy performed, as intraconjunctival neoplasia, or conjunctival intraepithelial neoplasia (CIN).

The majority of cases (43.6%) had no identifiable risk factors. 20.5% had a history of HPV, 18% had a history of excessive sun exposure, 10.3% had a history of smoking, and 7.6% of patients were HIV positive (Table 1 and Chart 2).

Table 1: Demographic data and diagnosis of OSSN patients treated with IFN α-2b.

Age (Years)	61 ± 16 (17-84)
Eye	
Right	21 (53.8%)
Left	18 (46.2%)
Gender	
Female	14 (35.9%)
Male	25 (64.1%)
Time of use (Months)	5 ± 2 (2-11)
Diagnosis	
Intraconjunctival neoplasia	18 (46.4%)
In situ carcinoma	7 (17.8%)
Invasive carcinoma	14 (35.8%)
Associated risk factors	
None	17 (43.6%)
Smoking	4 (10.3%)
Sun exposure	7 (18%)
HIV	3 (7.6%)
HPV	8 (20.5%)

We identified 3 IFN α-2b treatment groups: topical (N = 15) (Figure 1), intralesional (N = 6) (Figure 2) and topical combined with surgery (N = 18) (Figure 3).

The average time of treatment with IFN α-2b was 5 ± 2 months, being higher in the intralesional group (6.5 months mean use) than in the topical group (4.2 months mean use) (Table 2).

There were no adverse effects or systemic symptoms related to treatment with IFN α-2b. There were no postoperative complications.

None of the cases treated with intralesional IFN α-2b had a recurrence. Recurrence was observed in a total of five cases; two of these (5.2%) had been treated with topical IFN α-2b

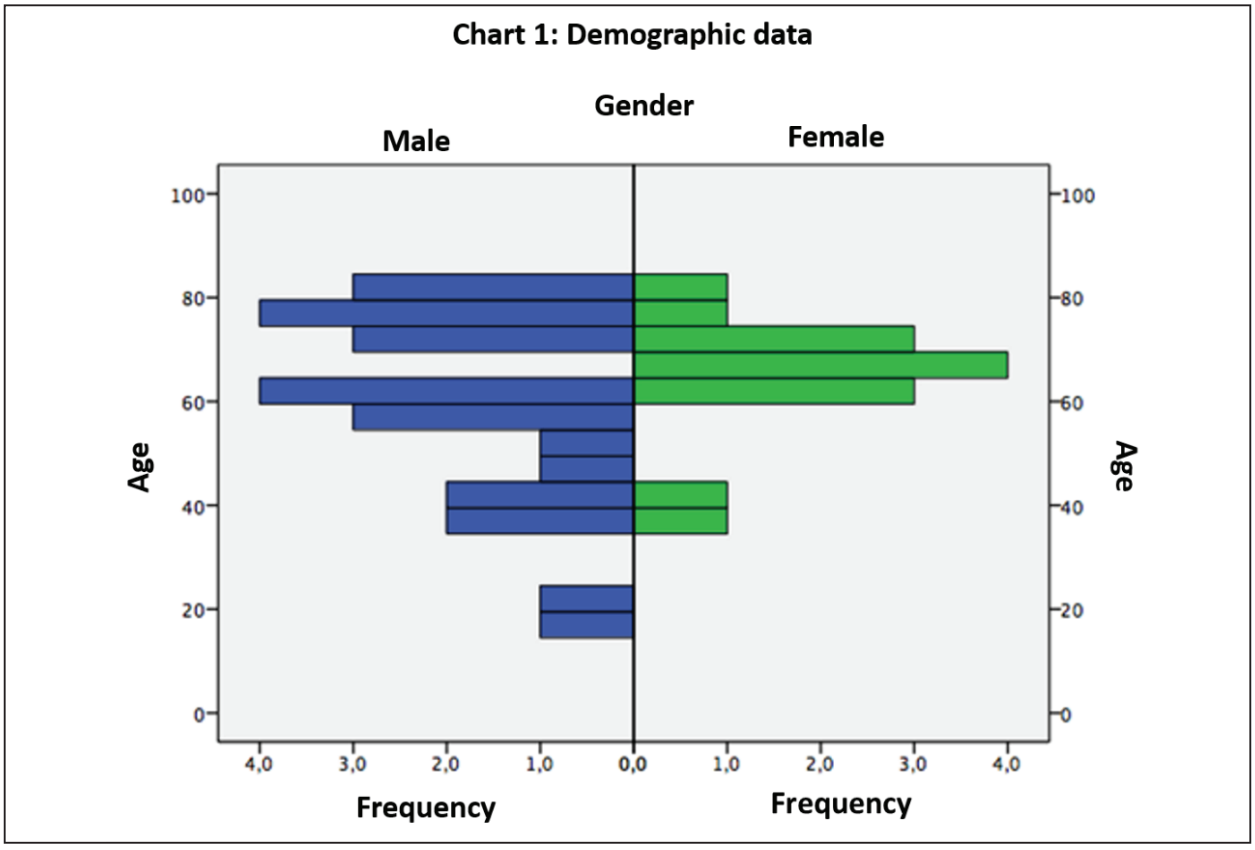
and three cases (7.7%) had been treated with a combination of surgery and IFN α-2b.

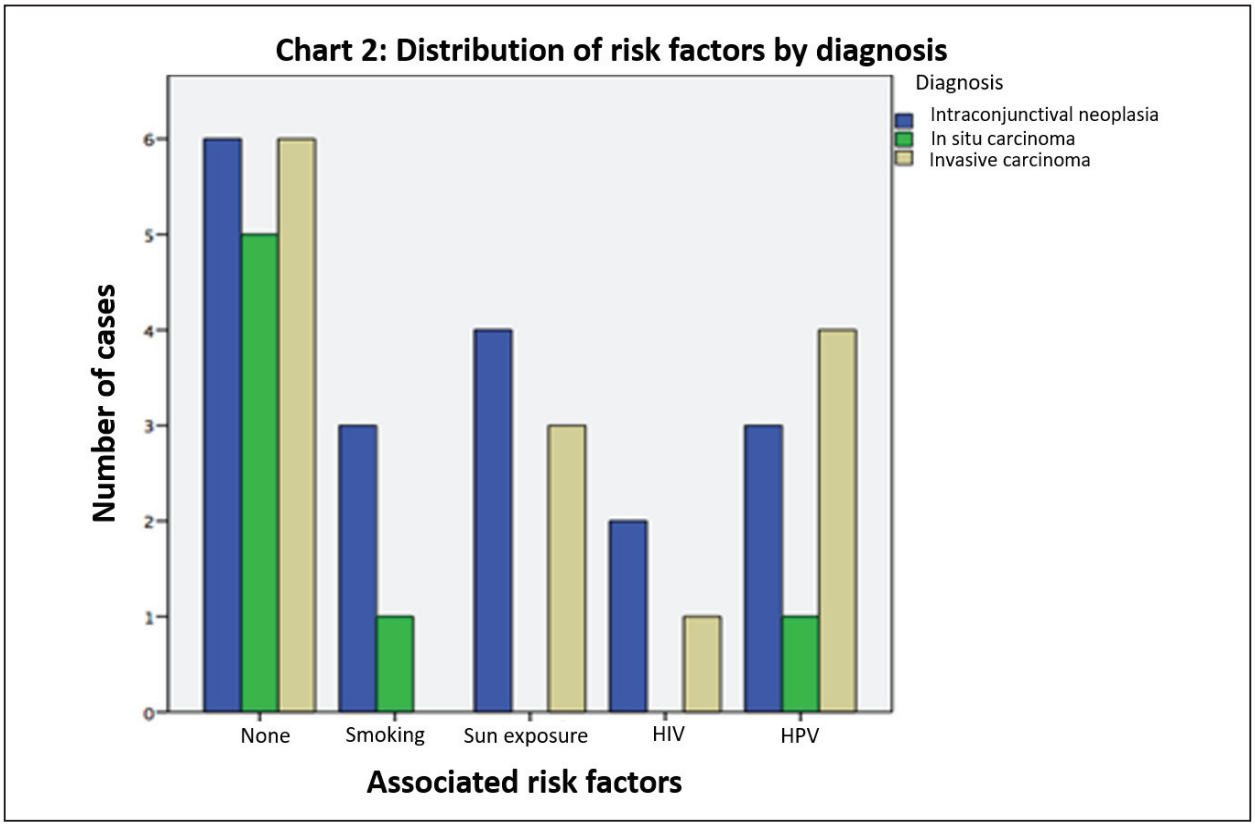
One of the patients treated with IFN α-2b combined with surgery was treated with orbital exenteration, and the other two patients refused any therapy. Both recurrent cases associated with topical therapy alone were given another cycle with good response, however, they were lost to follow up approximately 3 months after the beginning of the second cycle.

The clinical resolution with the use of IFN α-2b was evidenced between 0.5 and 10 months, being achieved in a total of 87.1% of all the patients.

Table 2: Results of treatment with IFN α-2b.

Group of treatment	Topical (N=15)	Intralesional (N=6)	Topical + Surgery (N=18)
Mean Age (Years)	60.5	62.5	61.8
Diagnosis			
Intraconjunctival neoplasia	7	2	9
In situ carcinoma	1	2	4
Invasive carcinoma	7	2	5
Recurrences	2 (5.1%)	0 (0%)	3 (7.7%)
Time of use (Months)	4.2 (2-9)	6.5 (4-11)	6 (2-10)
Time of follow up (Months)	17.8 (6-34)	15.2 (6-21)	17.5 (6-36)





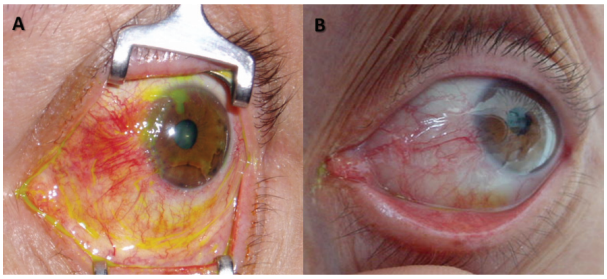


Figure 1: Ocular surface squamous neoplasia (OSSN) treated with topical IFN α-2b **A:** Before treatment. **B:** 10 months post-treatment.

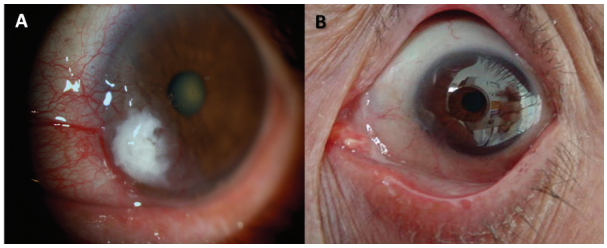


Figure 2: OSSN treated with intralesional/ subconjunctival IFN α-2b. **A:** Before treatment. **B:** 8 months post-treatment.

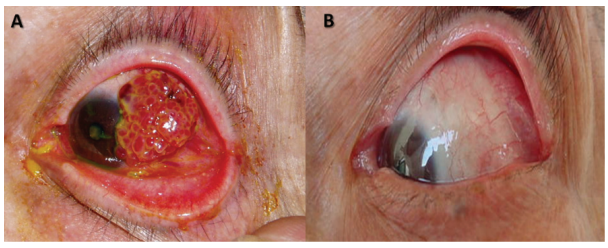


Figure 3: OSSN treated with topical IFN α-2b and Surgery **A:** Before treatment. **B:** 9 months post-treatment.

Discussion

In our study, the average age of diagnosis of OSSN was 61±16 years, with a male predominance. This is similar to what has been described in previous studies (Kamal et al,2015). Although most of the cases did not present identifiable risk factors, we were able to find risk factors such as smoking (10.3% of cases), excessive sun exposure (18%), HPV history (20.5%), and HIV (7.6%). All these have been previously described in different studies as factors associated with the etiology of OSSN (Karp et al, 2010; Fernandes et al., 2014; Kamal et al, 2015).

OSSN are generally treated with extensive surgical excision and cryotherapy. This may lead to limbal stem cell deficiency and high rates of recurrence, astigmatism, and symblepharon (Karp et al, 2010; Moon et al, 2016). In patients with large OSSN lesions at the limbus, or recurrent lesions, this form of treatment is especially complicated (Karp et al, 2010). Because of this, various local chemotherapies have been studied, such as the use of IFN α-2b.

Topical ophthalmic treatment with IFN α-2b is the preferred route of administration, due to the unnecessary application of injections that can produce systemic adverse effects (Fernandes et al, 2014). However, it requires a longer course of treatment to achieve full clinical resolution (Karp et al, 2010), needing patient cooperation and cooling of the medication (Karp et al, 2010; Fernandes et al., 2014). The subconjunctival / perilesional application is presented as a cost-effective treatment alternative, especially for the treatment of large tumors, in which case the topical application may not achieve sufficient penetration (Karp et al, 2010; Fernandes et al, 2014).

In our series, the mean time of use of topical IFN α-2b was 4.2 months; which is similar to the 12 to 14 weeks described in the literature (Karp et al, 2010; Nanji et al, 2014). However, we found a greater average time of use of subconjunctival/perilesional IFN α-2b as evidenced in previous studies (Karp et al, 2010). This may be due to the retrospective and non-randomized nature of the cases, leaving the subconjunctival/perilesional treatment to tumors larger than those treated topically and, therefore, requiring a higher total dose and treatment time for its resolution.

Treatment with topical IFN α-2b has been reported safe and well tolerated, with no side effects in most cases (Boehm and Huang, 2004; Sturges et al, 2008). Minor side effects are mild conjunctival hyperemia and follicular conjunctivitis (Schechter et al, 2008), not evidenced in our series. All adverse reactions tend to resolve once the treatment is discontinued (Fernandes et al, 2014). With the subconjunctival injection of IFN α-2b, mild systemic adverse effects may occur such as flu-like symptoms, myalgias, and fever. However, these are usually mild and well tolerated (Karp et al, 2010). No cases of death or carcinogenic side effects have been reported with the ocular use of IFN medication (Fernandes et al, 2014).

In our series, there was no evidence of adverse effects to the drug in its different modalities of application.

A recurrence rate of 5.1% was observed in cases treated with topical IFN α-2b alone, with an average follow-up of 17.8 months. The recurrence rates reported in the literature for this treatment modality range from 0% to 17% depending on the follow-up time (Nanji et al, 2014). In our study, there were no cases of recurrence with subconjunctival/perilesional IFN α-2b treatment at 15.2 months of follow-up. This is lower than that reported by Nanji et al (2014) of 3% at 1 year of follow-up. This may be due to the small number of patients who were treated only with subconjunctival/ perilesional IFN α-2b. The group treated with a combination of IFN α-2b and surgery had

a recurrence rate of 7.7% at 17.5 months of average follow-up time in our study.

We demonstrated a success rate of 87.1% in our patients treated with IFN α-2b. This is concordant with previous studies (Karp et al, 2010; Nanji et al, 2014; Galor et al, 2010; Galor et al, 2015).

These results should be interpreted considering the limitations of our study. Largely due to it being a retrospective study, it has selection biases since more aggressive treatments were indicated to lesions with clinically greater extension. Therefore, it would be interesting to know the evolution of the disease with these three forms of treatment compared to conventional surgical treatment in a prospective way.

Conclusions

The use of IFN α-2b is effective for the treatment of ocular surface squamous neoplasia since a high success rate (87.1%) was found with a low incidence of recurrence (5 patients), with no complications reported during the follow-up period. It is a viable alternative to conventional treatment since it provides immune-reduction of the tumor, allows synergy with the surgical treatment, and can even be used as a monotherapy in some cases as well.

References

Boehm MD, Huang AJ (2004). Treatment of recurrent corneal and conjunctival intraepithelial neoplasia with topical interferon alfa 2b. Ophthalmology; 111:1755-61.

Bracarda S, Eggermont A, Samuelsson J (2010). Redefining the role of interferon in the treatment of malignant diseases. Eur J Cancer; 46:284-297.

de la Cruz Aguiló RI, Duch-Samper A, Hernández Pérez D, Marí Cotino J (2014). Conjunctival intraepithelial neoplasia. Interferon as a rescue therapy after failure of mitomycin C. Arch Soc Esp Oftalmol; 89(11):463-5

Fernandes BF, Nikolitch K, Coates J, Novais G, Odashiro A, Odashiro PP, Belfort RN, Burnier MN Jr (2014). Local chemotherapeutic agents for the treatment of ocular malignancies. Surv Ophthalmol; 59(1):97-114.

Fraunfelder FT, Wingfield D (1980). Therapy of intraepithelial epitheliomas and squamous cell carcinoma of the limbus. Trans Am Ophthalmol Soc; 78:290–300.

Galor A, Karp CL, Chhabra S, et al (2010). Topical interferon alpha 2b eye-drops for treatment of ocular surface squamous neoplasia: a dose comparison study. Br J Ophthalmol; 94:551-4.

Galor A, Garg N, Nanji A, Joag M, Nuovo G, Palioura S, Wang G, Karp CL (2015). Human Papilloma Virus Infection Does Not Predict Response to Interferon Therapy in Ocular Surface Squamous Neoplasia. Ophthalmology; 122(11):2210-5.

Kamal S, Kaliki S, Mishra DK, Batra J, Naik MN (2015). Ocular Surface Squamous Neoplasia in 200 Patients: A Case-Control Study of Immunosuppression Resulting from Human Immunodeficiency Virus versus Immunocompetency. Ophthalmology; 122(8):1688-94.

Karp CL, Galor A, Chhabra S, Barnes SD, Alfonso EC (2010). Subconjunctival/perilesional recombinant interferon α2b for ocular surface squamous neoplasia: a 10-year review. Ophthalmology; 117(12):2241-6.

Lee GA, Hirst LW (1995). Ocular surface squamous neoplasia. Surv Ophthalmol; 39:429–450.

Maskin S (1994). Regression of limbal epithelial dysplasia with topical interferon. Arch Ophthalmol; 112:1145-1146.

Mata E, Conesa E, Castro M, Martínez L, de Pablo C, González ML (2014). Carcinoma epidermoide conjuntival: respuesta paradójica al colirio interferón. Arch Soc Esp Oftalmol; 89(7):293-6.

Moon CS, Nanji AA, Galor A, McCollister KE, Karp CL (2016). Surgical versus Medical Treatment of Ocular Surface Squamous Neoplasia: A Cost Comparison. Ophthalmology; 123(3):497-504.

Nanji AA, Moon CS, Galor A, Sein J, Oellers P, Karp CL (2014). Surgical versus medical treatment of ocular surface squamous neoplasia: a comparison of recurrences and complications. Ophthalmology; 121(5):994-1000.

Poothullil AM, Colby KA (2006). Topical medical therapies for ocular surface tumors. Semin Ophthalmol; 21:161–169.

Schechter BA, Koreishi AF, Karp CL, et al (2008). Longterm follow up of conjunctival and corneal intraepithelial neoplasia treated with topical interferon alfa-2b. Ophthalmology; 115:1291-6.

Scott IU, Karp CL, Nuovo GJ (2002). Human papillomavirus 16 and 18 expression in conjunctival intraepithelial neoplasia. Ophthalmology; 109:542–7.

Shields CL, Demirci H, Karatza E, Shields JA (2004). Clinical survey of 1643 melanocytic and nonmelanocytic conjunctival tumors. Ophthalmology; 111:1747–54.

Sturges A, Butt AL, Lai JE, et al (2008). Topical interferon or surgical excision for the management of primary ocular surface squamous neoplasia. Ophthalmology; 115:1297-302.

Tabin G, Levin S, Snibson G, et al (1997). Late recurrences and the necessity for long-term follow-up in corneal and conjunctival intraepithelial neoplasia. Ophthalmology; 104:485–92.