Treatment of conjunctival squamous neoplasias with interferon alpha 2b

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INTRODUCTION

Conjunctival intraepithelial neoplasia (CIN) is a precancerous lesion that occurs in exposed areas of bulbar conjunctiva with frequent involvement of the adjacent corneal epithelium. CIN is the most common tumor of the ocular surface [1]. Its incidence can vary from 0.13 to 1.9/100,000 inhabitants, depending on geographical location [2]. Clinical differentiation between CIN and another limbal lesions is based on characteristic clinical features [3]. Squamous cell neoplasia of the ocular surface can occur as a localized lesion confined to the surface epithelium (conjunctival intraepithelial neoplasia or dysplasia), currently called CIN, or as a more invasive squamous cell carcinoma that has broken through the basement membrane and invaded the underlying stroma. This second situation is termed squamous cell carcinoma (SCC) [4]. It has been found that most squamous cell neoplasia is related to human papillomavirus infection of the conjunctival epithelium, and this is most certain in patients with bilateral squamous cell neoplasia and in immunosuppressed patients who develop this disease [2, 5].

Conjunctival intraepithelial neoplasia (CIN) is a precancerous lesion...
usually at the limbus in the interpalpebral fissure and less commonly in the fornix or palpebral conjunctiva [3, 4, 6]. Some authors continue to describe the lesion as conjunctival papilloma [7-9]. The same conjunctival neoplasia may be seen in the conjunctiva of the lacrimal sac [8]. The limbal lesion may extend for a variable distance into the epithelium of the adjacent cornea. In this situation, more authors have denominated the disease conjunctiva-cornea intraepithelial neoplasia [6, 10]. In extreme cases, the invasion may be around two or three quadrants of the limbus [6]. White plaques of leukoplakia may be present on the surface of the lesion secondary to a hyperkeratosis [3, 4, 6]. An excisional biopsy is not absolutely necessary for the diagnosis of CIN [3]. The diagnosis may be made by the clinical appearance. Histopathologically, the lesion may be classified as mild CIN if a partial thickness replacement of the epithelium by abnormal epithelial cells is present. Severe CIN is characterized by a noticeable, nearly full-thickness replacement of epithelial cells by similar abnormal cells. The lesion is designated carcinoma in situ when a full thickness replacement by abnormal cells is present [4]. Squamous cell carcinoma is the denomination used when abnormal epithelial cells extend through the basement membrane, gaining access to the conjunctival stroma, as found in the histological study. The differences between the two entities are histological. However, clinically invasive squamous cell carcinoma is generally larger and more elevated than CIN [4]. Highly extensive epithelial neoplasias with aspects of squamous carcinoma may turn out to be only a CIN after the histological confirmation [6].

MANAGEMENT OF CIN

The no-touch technique of excision and cryotherapy is the classic approach to the treatment of well-localized CIN [4]. However, studies show a 53% recurrence rate in pathology studies that revealed involved margins and a 5% recurrence rate in pathology studies that confirmed clear margins [3]. In extensive lesions, surgical excision is difficult, and additional procedures have been employed. Extensive resections in very extensive CIN may produce a limbal stem deficiency [6]. Adjuvant radiation has the potential complications of cataracts, scleral necrosis, corneal rupture, scarring of the cornea and conjunctiva, moderate to severe conjunctivitis, and loss of lashes [11]. Topical chemotherapy with mitomycin C (MMC) 0.02%-0.04% [12-16] has been used to prevent recurrences, while exenteration is the choice in highly invasive squamous cell carcinomas [17].

MMC has been used effectively as primary treatment of CIN with reported success rates of 85% [18] and 100% [19]. Another large study has shown topical MMC to be an efficient treatment for most but not all cases of CIN [20]. Tumor regrowth occurred in approximately 17% of the cases [20]. Possible complications of topical MMC include superficial punctate epithiopath [4], conjunctival hyperemia [18, 20], pain [18], allergy [20, 1], corneal-scleral melting [4, 18-20], disturbance of tear film stability, punctal stenosis [21], goblet cell loss, squamous metaplasia [18, 22], and limbal stem cell depletion [16, 18, 20, 23]. Edema and endothelial apoptosis have been observed in experimental models [24]. MMC toxicity appears to be dose-dependent, increasing with the repetition of treatment cycles.

To prevent these possible severe side effects during long-term treatment with topical MMC, interferon (INF) alpha 2b has been employed in the management of CIN. During the last decade, it has been used in subconjunctival injections combined with subsequent topical eye drops. Topical INF alpha 2b alone has also been successfully used in the treatment of these neoplasias [11]. Topical INF alpha 2b was shown to have no corneal or conjunctival toxicity [25]. The accumulative experience of this treatment modality is based on isolated cases or very short series. In this report, we review all documented primary or recurrent cases of CIN treated with intralesional and/or topical INF alpha 2b. The aim of the study was to report on the safety and effectiveness of this therapy to help clinicians choose the best way of administering INF for treatment of the CIN.

METHODOLOGY OF THE STUDY

All studies reporting on this topic in the Medline/PubMed database (1987-April 2007) are described [6-10, 26-45]. “Interferon alpha 2b” and “conjunctival intraepithelial neoplasia” were the key words for the search. The studies’ references, as original articles, were also reviewed. Our personal published experience is also included [6, 26].

INTERFERON: MECHANISM OF ACTION

Interferon alpha is a cytokine with antiviral, immunomodulating, and antineoplastic activity. Endogenous interferon alpha is produced and secreted mainly by peripheral blood leukocytes in response to viral infection [46]. The precise mechanism of action of interferon is unknown but appears to be complex, and the resultant activities seem to be interrelated. Its binding at specific membrane receptors on the cell surface triggers a cascade of biologic modulation and pharmacologic effects such as induction of certain enzymes, suppression of cell proliferation, enhancement of the phagocytic activity of macrophages, augmentation of specific cytotoxicity of
lymphocytes for target cells, and inhibition of virus replication in virus-infected cells [47]. Some or all of these effects may be interrelated, and this could explain its antiviral and antineoplastic effects [46]. The relationship between human papilloma virus (HPV) and squamous neoplasia of the uterine cervix treated with interferon alpha may explain the effectiveness of INF alpha in CIN, because HPV is suspected as an etiologic agent [2, 5, 45].

Interferon alpha 2b is a purified interferon-alpha protein produced by recombinant DNA techniques (Escherichia coli strains). It contains 165 amino acids and has a molecular weight of approximately 19,000 daltons. In position 23 there is an arginine group. It is approved for the treatment of chronic hepatitis B and C, malignant melanoma, hairy cell leukemia, chronic myelogenous leukemia, multiple myeloma, follicular lymphoma, and carcinoid tumor [48].

INTERFERON ALPHA 2b PREPARATION FOR TOPICAL AND INTRALESIONAL ADMINISTRATION

All authors reviewed used 1 million IU/ml INF alpha 2b ophthalmic preparation as a topical treatment of CIN. These eyedrops are not marketed. We prepared the medication from a dilution of Intron A® 10 million IU/ml (Schering Plough, Spain) in water for injection [6, 26]. Other authors [27-29, 45] prepared the dilution with balanced salt solution. Kobayashi et al. [30] prepared a subconjunctival injection of 3 million IU/ml in distilled water and subsequently as 1 million IU/ml as eye drops.

After obtaining informed consent, patients were supplied with a 2-week course divided into two 2-ml bottles of ophthalmic solution. Patients were instructed in eye-drop administration. They were instructed to refrigerate the preparation between uses, and the ophthalmic solution was discarded 7 days after opening it [6, 26].

DOSAGE

One drop four times a day of 1 million IU/ml ophthalmic solution, until clinical resolution of the lesion or until the lesion appeared non-responsive, was the main dosage used [6, 26, 31, 45]. Sometimes the authors described the continuation of treatment for 2 [31, 45] to 4 weeks [32, 33] after the lesion had resolved. Only one patient was treated for a long-term period (8 months) after a recurrence of conjunctival squamous cell papilloma previously treated with INF alpha 2b for 2 weeks [34]. In one unresponsive patient, the dosage was increased to six times a day [45]. Intralesional injections of INF alpha 2b have also been described [31, 45] (tables I and II).

COST

The price of one vial of Intron A 10 million IU is 50 euros. This is the cost of approximately 1 month of treatment. Esquenazi et al. [33] calculated the cost to be $300 per treatment, which is two and three times more expensive than MMC and 5-FU, respectively, but the effectiveness and safety of INF outweighs this increase in cost. If there are no recurrences, as advertised, additional savings are obtained when there is no need for a surgical resection, which is an expensive procedure.

EFECTIVENESS OF INTERFERON ALPHA 2b

We found 66 patients treated with interferon alpha 2b subconjunctivally and/or topically for the treatment of CIN (tables I and II). In 1987, Lass et al. [7] used intramuscular INF alpha N-1 to treat recurrent conjunctival papilloma, and three out of five patients had recurrences of lesser severity. Maskin [35] was the first author to administer topical INF alpha 2b twice daily with slow tapering, and after 2 months of treatment, clinical resolution was obtained. There are some series of patients with good results at follow-up (tables I and II). The largest series is described by Holcombe et al. [45], who treated ten recalcitrant ocular surface squamous neoplasia cases that had been treated previously with topical MMC, none of whom had a recurrence at follow-up. Nemet et al. [29] treated three cases of recurrent CIN with subconjunctival and topical INF alpha 2b, with no recurrences. Other authors [6, 9, 10, 26, 30, 31, 33, 39, 40] have published case reports of successful treatment of one or two patients treated with INF alpha 2b alone or combined with subconjunctival administration. One case in a black pediatric patient refractory to treatment with INF alpha 2b was successfully treated with intraoperative MMC [45] (tables I and II).

Only Chen et al. [42] described one case report of a patient treated only with subconjunctival injection without topical treatment for bilateral papilloma CIN without recurrence for the subtotal excision treated with INF alpha 2b intralesionally in the right eye. In the left eye, total excision was done without INF, and recurrence occurred 10 months after surgery. Topical INF alpha 2b was the only pharmacologic treatment in 45 out of 71 patients affected by CIN. The average follow-up was 13 months (range, 3-40). It has been used combined with subconjunctival injection in 21 patients.

The tumoral mass was noted to regress early, in 1 [35], 2 [30, 32], or 3 weeks [31] after initiating INF alpha 2b treatment, and then it continuously decreased in size. There was one exception described in a case of increased CIN volume,
Table I
Treatment with topical and subconjunctival interferon alpha 2b (chronological order).

<table>
<thead>
<tr>
<th></th>
<th>Diagnosis</th>
<th>Previous excision or biopsy proved</th>
<th>Previous topical MMC</th>
<th>Subconjunctival INF alpha 2b (time)</th>
<th>Topical 1 million IU/ml INF alpha 2b (time)</th>
<th>Complete tumor regression (time)</th>
<th>Follow up (time after complete tumor regression)</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hu et al., 1998 [31]</td>
<td>1 Corneolimbal squamous dysplasia or carcinoma in situ</td>
<td>No</td>
<td>No</td>
<td>3.10^6 IU/week (2 weeks)</td>
<td>1 drop qid (10 weeks)</td>
<td>2 months</td>
<td>10 months</td>
<td>0</td>
</tr>
<tr>
<td>Hawkins et al., 1999 [41]</td>
<td>1 Recurrent squamous papilloma</td>
<td>Yes</td>
<td>Yes</td>
<td>6-6.5x10^6 IU intraoperative injections into the conjunctival margins</td>
<td>1 drop qid (2 weeks after each operation)</td>
<td>No</td>
<td>–</td>
<td>Recurrence after each operation. No recurrence (30-month follow-up) after posterior treatment with intraoperative MMC to the involved conjunctiva</td>
</tr>
<tr>
<td>Vann and Karp, 1999 [32]</td>
<td>6 Recurrence (n=2) or histologically proven CIN</td>
<td>Yes</td>
<td>No</td>
<td>3.10^6 IU/0.5 ml/week (1 week) if minimal response then 3.10^6 IU/0.5ml/2-3 times/week (until CR)</td>
<td>1 drop qid (1 month after CR)</td>
<td>4.5 weeks (3-6 weeks)</td>
<td>7.2 months (range, 2-11)</td>
<td>0</td>
</tr>
<tr>
<td>Parulekar et al., 2003 [8]</td>
<td>1 Recurrent lacrimal papilloma</td>
<td>Yes</td>
<td>No</td>
<td>3.10^6 IU/1 ml (single injection)</td>
<td>1 drop qid (2 months)</td>
<td>4 weeks</td>
<td>12 months</td>
<td>0</td>
</tr>
<tr>
<td>Kobayashi et al., 2002 [30]</td>
<td>1 Recurrent CIN</td>
<td>No</td>
<td>No</td>
<td>3.10^6 IU/1 ml (2 weeks)</td>
<td>1 drop qid (12 weeks)</td>
<td>2 weeks</td>
<td>1 year</td>
<td>0</td>
</tr>
<tr>
<td>Morgentstern et al., 2003 [34]</td>
<td>1 Conjunctival squamous papilloma (CSP)</td>
<td>No</td>
<td>No</td>
<td>0.3 ml (6.10^6IU ml)</td>
<td>1 drop qid (2 weeks)</td>
<td>2 weeks</td>
<td>6 weeks</td>
<td>1</td>
</tr>
<tr>
<td>R*</td>
<td>Recurrence of CSP</td>
<td>No</td>
<td>No</td>
<td>0.3 ml (6.10^6IU ml)</td>
<td>1 drop qid (8 months)</td>
<td>6 weeks</td>
<td>18 months</td>
<td>0</td>
</tr>
<tr>
<td>Toledano et al., 2003 [37]</td>
<td>4 Recurrent CIN</td>
<td>Yes</td>
<td>Yes (n=3) No (n=1)</td>
<td>3.10^6 IU/0.5ml/week (2 months) then every 2 weeks for 2 months then every month until CR (n=1)</td>
<td>1 drop qid (1 month) then 1 drop bid (1 month) then 1 drop qid (1 month)</td>
<td>Range, 1-2 months</td>
<td>20.25 months (range, 16-24 month)</td>
<td>0</td>
</tr>
<tr>
<td>De Keizer et al., 2003 [43]</td>
<td>1 Recurrent conjunctival papilloma</td>
<td>Yes</td>
<td>Not MMC Yes 5-FU eyedrops</td>
<td>Not subconjunctival INF alpha 2b subcutaneous (6 months)</td>
<td>2.8x10^6 IU/48 h (1 year)</td>
<td>Not specified</td>
<td>22 months</td>
<td>1 Retreatment with INF alpha 2b 2.8x10^6x8 months gave 84 months disease-free</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>2.8x10^6 IU/48 h</td>
<td>3 months</td>
<td>91 months</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

n: Number of patients; MMC: Mitomycin C; IM: intramuscular; bid: twice a day; qid: four times per day; sid: six times per day; CR: clinical resolution; oid: once a day; R*: retreatment of the same patient.
after 15 days of treatment, but after continuing therapy, remarkable progressive regression was detected with total remission after 60 days of treatment [26] (tables I and II).

**TOXICITY OF TOPICAL AND SUBCONJUNCTIVAL INTERFERON ALPHA 2b**

Administration of interferon alpha 2b ophthalmic solution is well tolerated (table III). Applied topically, this drug has few side effects: hyperemia [38] and follicular conjunctivitis [8, 27], keratitis [43], minor irritation [45], and redness [26], which resolve after cessation of treatment. No known carcinogenic potential and no corneal toxicity [25] is related to topical INF alpha 2b (table III). However, after subconjunctival injection, systemic discomfort [42], such as transient overnight fevers and myalgias, has been described [32, 42], which were alleviated with analgesics-antipyretics (table IV). These symptoms suggest some degree of systemic absorption. Nevertheless, these side effects are less severe than the flu-like syndrome, hypotension, tachycardia, somnolence, and anorexia reported with INF alpha systemic administration [47].

**DISCUSSION**

The standard treatment for CIN is surgery. Because of the high risk of recurrence depending on the clear tumor margins, adjuvant treatment with cryotherapy, radiotherapy, or certain antineoplastic drugs has been used. Topical MMC and 5-fluorouracil have been used to reduce recurrence rates when used as an adjunct to surgical excision; however, their use can be associated with pronounced ocular surface toxicity [16, 45].

Topical INF alpha 2b is well tolerated. Subconjunctival administration presents more side effects, as is described above and in tables III and IV. Schechter [27] reported local conjunctival injection and follicular conjunctivitis in four of seven patients. It was proposed, however, that the folliculitis was likely to be caused by the vehicle, which contained benzyl alcohol 0.09%, glycerin, and human albumin, and not the INF alpha 2b itself [45].

Topical INF alpha 2b, sometimes combined with subconjunctival INF alpha 2b, seems to be effective as primary treatment for CIN, in recurrent cases but also in retreatment after recurrence when INF has been used previously for a short period of time (tables I and II). Six patients out of 66 treated with subconjunctival and/or topical INF alpha 2b had recurrences. Two of them were successfully retreated with topical INF alpha 2b. Another one achieved complete remission after intra- and perioperative MMC.

For INF alpha 2b topical treatment, the average time to complete tumor response was 11 weeks (range, 2-59). The average follow-up was 13.3 months (range, 3-40), and only three patients out of 45 had recurrences. One of them was successfully retreated with topical INF alpha 2b.

For INF alpha 2b subconjunctival and topical treatment, the average time to complete tumor response was 5.5 weeks (range, 2-12). The average follow-up was 22.7 months (range, 5-60), and only three patients out of 21 had recurrences. One of them was successfully retreated with topical INF alpha 2b. Another one achieved complete remission after intra- and perioperative MMC [41].

Karp et al. [36] found that the time to clinical resolution using INF alpha 2b was longer (11.6 weeks) than in their own previous experience [32] with the combined intralesional and topical interferon (4.5 weeks), but that INF alpha 2b treatment involved fewer side effects. One recurrence after treatment with 2 weeks of INF alpha 2b...
### Table II
Treatment with topical interferon alpha 2b alone (chronological order).

<table>
<thead>
<tr>
<th>n</th>
<th>Diagnosis</th>
<th>Previous excision or biopsy proved</th>
<th>Previous topical MMC</th>
<th>Sub-conjunctival INF alpha-2b (time)</th>
<th>Topical 1.10^6 IU ml INF alpha 2b (time)</th>
<th>Complete tumor regression (time)</th>
<th>Follow-up</th>
<th>Recurrence (time after complete tumor regression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Recurrent limbal epithelial dysplasia</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>1 drop bid and slowly tapered (2 months)</td>
<td>2 months</td>
<td>9 months</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>Recurrent CIN</td>
<td>Not specified</td>
<td>Not specified</td>
<td>No</td>
<td>1 drop bid (2 months) and 1 drop bid (3 more months)</td>
<td>Not specified</td>
<td>19 months</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Histologically proven CIN or recurrences</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>1 drop qid with or without tapering (from 1 to 5.5 months or 1 month after CR)</td>
<td>11.6 weeks (range, 4-22)</td>
<td>17.6 months (range, 7-28)</td>
<td>1 patient (1 year) Retreatment with clinical resolution in 6 weeks (tumor-free for 8 months of follow-up)</td>
</tr>
<tr>
<td>7</td>
<td>Primary CIN</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>1 drop qid or sid (57-120 days or 1 month after CR)</td>
<td>77.0±59.2 days (range, 28-188)</td>
<td>12.4±2.5 months (range, 9-16)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Benign conjunctival papilloma</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>1 drop qid until CR</td>
<td>9 weeks (range, 6-12 weeks)</td>
<td>29 months (range, 18-40 months)</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>CIN</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>1 drop qid (11 days)</td>
<td>Not specified</td>
<td>10 months</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Recurrent CIN</td>
<td>Yes</td>
<td>Yes (n=4)</td>
<td>No (n=3)</td>
<td>1 drop qid (14.1 weeks; range, 6-24)</td>
<td>14.5 weeks (range, 5-24) in 6/7 patients</td>
<td>11.7 months (8-17 months) in 6/7 patients</td>
<td>2 patients (7 months; range, 2-12 months)</td>
</tr>
<tr>
<td>1</td>
<td>Suggestive squamous cell carcinoma</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>1 drop qid (70 days)</td>
<td>44 days</td>
<td>6 months</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>Moderate to severe dysplasia of corneal/conjunctival mass</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>1 drop qid (3 months)</td>
<td>84 days</td>
<td>3 months</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>CIN</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>1 drop qid (1 month after CR)</td>
<td>4 months</td>
<td>2 years</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Histologically proven CIN</td>
<td>Yes, amniotic membrane graft</td>
<td>No</td>
<td>No</td>
<td>1 drop five times daily (6 weeks)</td>
<td>Yes</td>
<td>13.2±4.97 months</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Recalcitrant ocular surface squamous neoplasia</td>
<td>Yes (n=6)</td>
<td>No (n=4)</td>
<td>Yes (n=10)</td>
<td>24.4 weeks of topical INF alpha 2b (range, 6-51 weeks)</td>
<td>21.9 weeks (range, 6-59) in 8/10 patients</td>
<td>53.4 weeks (range, 26-84)</td>
<td>0 in 8/10 patients of clinical resolution</td>
</tr>
<tr>
<td>1</td>
<td>Primary CIN</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>1 drop qid (75 days)</td>
<td>75 days</td>
<td>1 year</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>Conjunctival papilloma</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>1 drop qid (2 weeks) (small pingeucula)</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>Primary CIN</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>1 drop qid (60 days)</td>
<td>60 days</td>
<td>6 months</td>
<td>0</td>
</tr>
</tbody>
</table>

n: Number of patients; MMC: Mitomycin C; IM: intramuscular; bid: twice a day; qid: four times per day; sid: six times per day; CR: clinical resolution; oid: once a day; R*: retreatment of the same patient.
was newly treated with topical INF alpha 2b for 8 months with success [34]. In general, it seems that the disadvantage of this form of treatment is the long duration. The only safe method of gauging when to stop the treatment is the disappearance of the lesion in the slit lamp examination. It is important to emphasize the importance of long-term follow-up for CIN patients because recurrences can occur anywhere from 33 days to 11.5 years [49], although most recurrent CIN occurs within 2 years of initial excision [50].

Vann and Karp [32] noted a dose-dependent response with the combined administration of subconjunctival and topical therapy for the treatment of CIN. The larger lesions required repeated subconjunctival/perilesional injections, but it is suggested that smaller or residual lesions would be amenable to topical therapy alone. Other authors have noted the influence of lesion size in the choice of therapy [51]. Many surgeons add adjunctive topical therapy to their surgical regimens for larger lesions [51]. In our experience [6, 26], all lesion sizes could be treated with topical INF alpha 2b as the primary treatment because it is an effective, noninvasive treatment alternative to surgery that increases quality of life and is low-cost. Today, no clear consensus on the best way to manage the disorder has been established, because long-term, well-designed studies are still needed.

When there is a recurrence after INF alpha 2b treatment, an alternative could be intraoperative MMC, as described by Hawkins et al. [41] in a pediatric patient.

Chen et al. [42] suggest that adjunctive therapy with INF alpha 2b may be needed for all lesions to lower the recurrence rate, particularly if surgical excision cannot ensure tumor-free margins; in larger tumors, topical INF alpha 2b might result in poor tumor regression because of insufficient drug penetration. Also, to avoid a large dose of intralesional INF alpha 2b, excisional biopsy to decrease tumor mass is suggested. However, it has been demonstrated that topical INF alpha 2b may be curative in treatment of these neoplasias [6].

This review aims to help the clinician in the decision for the therapy in cases of CIN. A medical alternative to surgery for the treatment of CIN would be of great benefit, especially in cases of recurrent disease, in which multiple surgical procedures could be avoided [32]. Further clinical studies are necessary to establish the exact place in therapy of interferon alpha 2b. This new chemotherapeutic modality is being used to avoid the operating room and to decrease the potential risk of limbal stem cell loss and scarring. To date, there are no comparative studies of this topical treatment to surgical resection plus cryotherapy in the literature. This therapy is especially recommended for patients who reject any surgical procedure, for patients

### Table III

<table>
<thead>
<tr>
<th>N</th>
<th>INF alpha 2b</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schechter et al., 1999 [39]</td>
<td>1</td>
<td>Topical</td>
</tr>
<tr>
<td>Karp et al., 2001 [36]</td>
<td>5</td>
<td>Topical</td>
</tr>
<tr>
<td>Schechter et al., 2002a [27]</td>
<td>7</td>
<td>Topical</td>
</tr>
<tr>
<td>Schechter et al., 2002b [44]</td>
<td>2</td>
<td>Topical</td>
</tr>
<tr>
<td>De Keizer et al., 2003 [43]</td>
<td>2</td>
<td>Topical</td>
</tr>
<tr>
<td>Morgenstern et al., 2003 [34]</td>
<td>1</td>
<td>Topical</td>
</tr>
<tr>
<td>Boehm and Hoang, 2004 [28]</td>
<td>7</td>
<td>Topical</td>
</tr>
<tr>
<td>Diaz-Valle et al., 2005 [40]</td>
<td>1</td>
<td>Topical</td>
</tr>
<tr>
<td>Esquenazi et al., 2005 [33]</td>
<td>2</td>
<td>Topical</td>
</tr>
<tr>
<td>Fuchsluger et al., 2006 [42]</td>
<td>5</td>
<td>Topical</td>
</tr>
<tr>
<td>Huerva et al., 2006 [6]</td>
<td>1</td>
<td>Topical</td>
</tr>
<tr>
<td>Huerva et al., 2007 [26]</td>
<td>1</td>
<td>Topical</td>
</tr>
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</table>
with mental retardation in whom a surgical procedure is very difficult, and in highly extensive cases for which a surgical procedure could produce limbal stem cell depletion [6]. As has been demonstrated in cases of recurrence, this therapy has a substantial advantage over a new tumor excision. The clinician and patient must weigh the balance of cost, duration of treatment, and possible side effects in deciding on the primary treatment of CIN with INF alpha 2b.

CONCLUSION

Considering the frequency of recurrence of the disease because of the difficulty of complete resection and the potential surgical complications associated with treating CIN with surgery and cryotherapy, we believe that a pharmacological alternative such as topical INF alpha 2b is cost-effective. This treatment is highly effective with minimal side effects, and it is inexpensive because it may preserve visual function, avoid surgical excision, and reduce healthcare costs.

Topical INF alpha 2b alone has shown high efficacy in well-localized and highly extensive cases of CIN. The absence of systemic symptoms after topical administration suggests the advisability of beginning the treatment of CIN with topical eye drops containing INF alpha 2b.

### REFERENCES


### Table IV
Systemic toxicity with intralesional interferon alpha 2b.

<table>
<thead>
<tr>
<th>N</th>
<th>INF α 2 b</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lass et al., 1987 [7]</td>
<td>5</td>
<td>No topical INF alpha 2b</td>
</tr>
<tr>
<td>Hu et al., 1998 [31]</td>
<td>1</td>
<td>Topical and subconjunctival</td>
</tr>
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<td>Vann et al., 1999 [32]</td>
<td>6</td>
<td>Topical and intralesional</td>
</tr>
<tr>
<td>Parulekar et al., 2002 [8]</td>
<td>1</td>
<td>Subconjunctival and topical</td>
</tr>
<tr>
<td>Kobayashi et al., 2002 [30]</td>
<td>1</td>
<td>Subconjunctival and topical</td>
</tr>
<tr>
<td>De Keizer et Wolff-Rouendaal, 2003 [43]</td>
<td>2</td>
<td>Systemic (subcutaneously)</td>
</tr>
<tr>
<td>Toledano-Fenandez et al., 2003 [37]</td>
<td>4</td>
<td>Topical and subconjunctival</td>
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<td>Chen et al., 2004 [12]</td>
<td>1</td>
<td>Perilesional injection</td>
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<td>Nemet et al., 2006 [29]</td>
<td>3</td>
<td>Topical or intralesional</td>
</tr>
</tbody>
</table>
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