

# Efficacy of Long-term Interferon-alpha Therapy in Adult Patients with Recurrent Respiratory Papillomatosis

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## 성인의 재발성 호흡기계 유두종증 환자에서 장기간 인터페론 치료의 유효성

남해성, 고원중, 서지영, 정만표, 권오정, 김호중

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**연구배경:** 재발성 호흡기계 유두종증은 기관을 따라 다발성 유두종이 반복적으로 재발하는 매우 드문 질환이다. 1980년대 이후, 소아의 재발성 유두종증에 보조적 치료로 인터페론이 사용되어 왔다. 그러나, 성인 환자에서의 유효성 등에 대하여는 많은 연구 등이 필요하다. 2002년 이후, 삼성서울병원에서는 성인의 재발성 호흡기계 유두종증 환자들에서 재발을 예방하기 위해, 인터페론을 사용하여 왔다. 이에 본 저자들은 재발성 호흡기계 유두종증 성인 환자에서 인터페론의 장기간 사용 효과를 알아보려고 하였다.

**방 법:** 기관지내시경과 조직학적으로 확인된 5명의 재발성 호흡기계 유두종증 환자에서 타 병원에서 치료한 기록 등을 포함한 의무기록 등을 조사하였다. 레이저 소작술을 포함한 치료적 기관지내시경 시술 후, 모든 환자는 2개월 간격으로 인터페론-알파 600만 단위를 피하주사 하였다. 추가적인 치료적 기관지내시경 시술은 추적 검사 중 환자의 증상 등을 확인하여 필요 시 시행하였으며, 기관지 내시경 또는 컴퓨터 단층 촬영 등을 추적 조사하였다.

**결 과:** 모든 환자들의 연령의 중앙값은 44세(범위 13~68세), 남녀비는 3 : 2, 유두종증 기간의 중앙값은 31년(범위 1~45년)이었다. 소아형과 성인형 유두종증은 각각 3명과 2명이었으며, 2명의 환자는 진단 당시 기관절개술을 시행 받았던 과거력이 있었다. 인터페론 치료기간의 중앙값은 56개월(범위 12~66개월)이었다. 인터페론 치료 후 2명의 환자는 12개월과 36개월에 각각 완전완화를 보였으며, 나머지 3명의 환자는 부분완화를 보여 레이저 치료의 횟수가 중요하게 감소하였다.

**결 론:** 재발성 호흡기계 유두종증 환자에서 인터페론의 보조적 치료의 적정 용량과 기간 등은 향후 더 많은 연구 등을 필요로 하며, 오랜 기간 지속된 성인의 재발성 호흡기계 유두종증 환자에서 2개월 간격의 인터페론의 치료는 안정적이며 효과적이다. (*Tuberc Respir Dis* 2008;65:390-395)

**Key Words:** Adjuvant therapy, Interferon-alpha, Recurrent respiratory papillomatosis

## Introduction

First described in the seventeenth century as a "wart in the throat", recurrent respiratory papillomatosis (RRP)<sup>1</sup> is a rare disease characterized by the growth and

relentless recurrence of benign squamous papillomas in the respiratory tract. The lesions most commonly involve the oral cavity, oropharynx, and larynx, and only 5% of these tumors extend more distally to involve the trachea<sup>2</sup>. Involvement of the lung parenchyma is rarer still, occurring in less than 1% of cases<sup>3,4</sup>. Malignant transformation into squamous cell carcinoma occurs in 3~5% of patients, and may be idiopathic or due to exposure to carcinogens, immunosuppressants, radiation, or smoking<sup>5-7</sup>.

The age distribution of RRP is bimodal, with juvenile onset (< 5 years) or adult onset (> 20 years), and the prevalence of this disease is about 3 to 5 per 100,000

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population<sup>8</sup>.

In general, no disease-specific definitive medical therapy is available for RRP. Therefore, standard treatment consists of endoscopic laser excision of all visible papilloma from affected areas of the respiratory tract, as warranted by the patient's symptoms. The disease is noted for its highly unpredictable course, with rapid growth, spread within the respiratory tract, spontaneous resolution, and the constant possibility of airway obstruction requiring urgent intervention to maintain patency<sup>9</sup>. Due to the clinical variability of RRP, several methods of adjuvant therapy have been reported, including interferon- $\alpha$  (IFN- $\alpha$ ), indole-3-carbinole, methotrexate, cidofovir, acyclovir, ribavirin, cis-retinoic acid, and photodynamic therapy<sup>10-15</sup>.

Since 2002, Samsung Medical Center's guidelines have mandated regular injection of IFN- $\alpha$  in adult patients with RRP. After initial laser therapy, patients receive subcutaneous injection of 6 million units of IFN- $\alpha$  every 2 months, and are evaluated regularly by bronchoscopy and/or computed tomography (CT).

To describe and evaluate the efficacy of long-term IFN- $\alpha$  therapy in adult patients with RRP, patient data were investigated in the present study.

## Materials and Methods

### 1. Patients

The study population included patients with RRP referred for laser therapy from January through December 2002. All patients were diagnosed by bronchoscopy and histopathology. The protocol was approved by the Institutional Review Board of Samsung Medical Center and patients gave their informed consent to use IFN- $\alpha$  as part of their adjuvant treatment for RRP. Patients' medical records were reviewed and clinical characteristics, number of laser treatments before and after IFN- $\alpha$  injection, adverse events of IFN- $\alpha$ , and clinical outcome were investigated.

### 2. Diagnostic procedure

Patients were evaluated by chest radiography, spi-

rometry, bronchoscopy, and biopsy at the time of referral. Bronchoscopy showed multiple wart-like papillomas scattered in the central airways, which showed a typical bunch-of-grapes appearance. Pathology confirmed the diagnosis of papilloma.

### 3. Technique of bronchoscopic intervention and IFN- $\alpha$ injection

All patients underwent bronchoscopic intervention with rigid bronchoscopy under general anesthesia. After induction of general anesthesia, patients were intubated with a rigid bronchoscope tube (Hopkins; Karl-Storz, Tuttlingen, Germany). A flexible bronchoscope (EVIS BF 1T240; Olympus, Tokyo, Japan) was then introduced through the rigid bronchoscope, and the tumor was mechanically removed by suction. Then, a 20 watt Nd-YAG laser (Model 1000; LaserSonics, Milpitas, CA, USA) was applied using a G56D noncontact fiber (LaserSonics) to cauterize the base of the papilloma and to control bleeding. Laser cauterization was minimized to prevent unnecessary injury to the normal mucosa and future development of new papilloma.

After bronchoscopic intervention, patients received subcutaneous injection of 6 million units of IFN- $\alpha$  (Roche, Basel, Switzerland) every 2 months until complete remission of RRP.

### 4. Follow-up procedure and definition of outcome

After laser therapy and IFN- $\alpha$  injection, patients were regularly evaluated by bronchoscopy every three to six months and/or chest CT every twelve months. In addition, further bronchoscopic intervention was carried out as needed to maintain airway patency.

Clinical outcome was evaluated based on patients' symptoms, chest radiography, bronchoscopy, and/or CT findings. Response to treatment was classified as complete, partial, or no remission, which were defined as no evidence of disease for at least 6 months, stable and reduced need of laser therapy, and the same or increased (aggravated recurrence) need of laser therapy after IFN- $\alpha$  injection, respectively.

## Results

### 1. Patient characteristics

The patient population consisted of five patients ranging in age from 13 to 68 years with a median of 44. Two patients were female. Three and two patients had juvenile-onset and adult-onset RRP, respectively. The duration of papillomatosis was 1 to 45 years with a median 31 years. Two patients had a history of tracheostomy at the time of referral. The clinical characteristics of the five patients are summarized in Table 1. At the time of referral, all patients showed normal chest radiography, and spirometric results were normal (patients 2, 4 in Table 1), mild obstructive pattern (patients 3,

5 in Table 1), and moderate obstructive pattern (patient 1 in Table 1), respectively.

### 2. Characteristics of papillomatosis

All patients showed laryngeal involvement of papilloma. Papillomas were distributed in the trachea in four patients, and lung parenchyma in one patient. Immunohistochemistry was carried out to detect HPV, but the results were negative in all patients. However, HPV cytopathic effect was observed in one patient (patient 2 in Table 1), who showed malignant transformation into squamous cell carcinoma after 18 months of IFN- $\alpha$  therapy. This patient underwent right upper lobe lobectomy.

Table 1. Patient characteristics

Patient	1	2	3	4	5
Gender	F	M	M	F	M
Age (years)	13	38	44	52	68
Pastmedical history	—	—	—	Hypertension, Thyroid nodule	Asthma
Family history	—	—	—	—	—
Smoking	Never	Never	Current	Never	Ex
Onset age (years)	3	2	13	7	68
Tracheostomy	—	+	—	+	—
Site of Lesion					
Larynx	+	+	+	+	+
Trachea	+	+	—	+	+
Lung	—	+	—	—	—
Cancer transformation	—	+	—	—	—



**Figure 1.** Representative photographs of papillomas following IFN- $\alpha$  therapy. Bronchoscopy of 38-year-old male patient showed a huge papilloma in the upper trachea (left). After laser treatment, IFN- $\alpha$  injection was started and the papilloma showed marked regression 4 (middle) and 5 years after (right) IFN- $\alpha$  injection.

Table 2. Response of IFN- $\alpha$ 

Patient	1	2	3	4	5
IFN start date	Feb. 2002	Feb. 2002	Oct. 2002	Nov. 2002	Dec. 2002
No. of laser sessions per year					
Before IFN	4	2,2	1	1,6	3
After IFN	1,5	1,4	0	1,4	1,6
Duration of IFN Tx (months)	36	66	12	58	56
Response					
CR	+		+		
PR		+		+	+

Tx: treatment; CR: complete remission; PR: partial remission.

### 3. Response to IFN- $\alpha$

Papillomas regressed after IFN- $\alpha$  injection in all patients. Representative photographs are shown in Figure 1.

After IFN- $\alpha$  therapy, two patients showed complete remission of papilloma for at least 6 months. During the median 38,5 months (range 31~46) of follow-up after the end of treatment, they showed no airway problems and no evidence of recurrence on bronchoscopy or CT. The other three patients showed partial remission and required less bronchoscopic intervention than before treatment. The number of laser treatments decreased from an average of 2,6 to 1,5 times per year after IFN- $\alpha$  therapy. The median durations of IFN- $\alpha$  therapy were 24 months (range 12~36) in complete responders and 58 months (range 56~66) in partial responders. Responses to treatment with IFN- $\alpha$  in the five patients are summarized in Table 2.

Two months after IFN- $\alpha$  therapy, three patients complained of fever and myalgia. However, these symptoms were transient and required only occasional acetaminophen. No other adverse events were associated with IFN- $\alpha$  treatment in the present study.

### Discussion

All five patients in the present study showed favorable responses to subcutaneous injection of 6 million units of IFN- $\alpha$  every 2 months. This result suggests that IFN- $\alpha$  maybe effective for the treatment of adult patients

with long-standing recurrent papillomatosis because the patients in the present study had a median disease duration of 31 years. In addition, long-term use of IFN- $\alpha$  resulted in complete remission of RRP in two of these patients and at least reduced the number of laser therapy sessions required.

In general, the presence of HPV DNA types 6 and 11 was implicated in the pathogenesis of RRP, which are the same viral types associated with genital condylomata<sup>16,17</sup>. These viral types can infect the entire respiratory tract, although the squamous-columnar junction of the larynx is the most common site of involvement<sup>18</sup>. Although RRP is relatively rare compared to genital condylomata, the genital tract appears to act as a reservoir for transmitting HPV to the respiratory tract, and exposure of the upper airway to HPV type 6 or 11 occurs frequently during life<sup>19</sup>. Juvenile-onset RRP has been reported to be associated with both vaginal delivery and delivery by cesarean section<sup>20</sup>. In addition, with regard to adult-onset RRP, oral sexual practices have been associated with a slightly higher risk for the development of papillomas<sup>21</sup>. However, the pathogenesis of this disease is still not fully understood.

Final conformation of RRP is histological. Histologically, papillomas appear as pedunculated masses of slender projections of non-keratinizing stratified squamous epithelium supported by a core of highly vascular connective tissue stroma. Cellular differentiation has been shown to be abnormal in papillomas, with altered expression and production keratins. The papillomatous lesions usually arise at anatomical sites that

contain juxtaposed epithelium<sup>22</sup>. In the present study, all patients was diagnosed as having multiple papillomatosis on bronchoscopy and papillomas on histopathological examination.

The basic method for treatment of RRP is surgical removal of the lesion by mechanical or laser debulking. However, repeated surgery is required due to the relentless recurrence of papillomas. Children require a mean of 4.1 to 4.4 procedures during their first year after diagnosis<sup>8</sup>. Therefore, we defined the complete remission as no evidence of disease for at least 6 months. Recurrence is known to be due to the persistence of viral DNA in normal-appearing epithelium<sup>23</sup>.

Because of relentless clinical variability of RRP, numerous adjuvant medical therapies are available to prevent recurrence. However, despite several multicenter trials, no definitive therapeutic modalities to prevent recurrence have yet been reported.

IFN- $\alpha$  has theoretical benefits of modulating both the immune system and epithelial development. Since the early 1980s, interferon has been used as an adjuvant agent in treating patients with RRP and is the most extensively investigated of these agents. However, debate is ongoing regarding the effectiveness of long-term IFN- $\alpha$  therapy, with even multicenter studies on the application of IFN- $\alpha$  as an adjuvant for RRP therapy providing contradictory results<sup>13,15</sup>. A recent study revealed the maximal effectiveness of IFN- $\alpha$  therapy in patients having RRP with HPV 6 as compared to HPV 11<sup>12</sup>. In addition, these results suggest that long-term IFN- $\alpha$  therapy (mean  $32.4 \pm 21.6$  months)<sup>12</sup> was more effective in preventing relapse than the a short course (0.5 or 1 year)<sup>13,15</sup> of injection. Accumulation of additional evidence, however, is required to determine the dosage and duration of IFN- $\alpha$  treatment suitable for patients with RRP.

IFN- $\alpha$  has various side effects, but these are usually transient. Thus, no need exists to discontinue IFN- $\alpha$  in most patients, except in those who develop antibodies against it<sup>24</sup>. In the present study, three patients complained of transient febrile sensation and myalgia, but their symptoms improved spontaneously or with admin-

istration of acetaminophen.

Our experience with long-term use of IFN- $\alpha$  in adult patients with RRP has provided valuable insight into the effects of this adjuvant agent. Injection of IFN- $\alpha$  was effective in adult patients with long-standing recurrent papillomatosis, achieving complete remission of RRP in two of five cases, and at least reducing the number of laser therapy sessions required in all patients. Further studies with larger numbers of cases are required to obtain generalized conclusions regarding the efficacy of long-term use of IFN- $\alpha$  in the treatment of patients with RRP.

## Summary

**Background:** Since the early 1980s, interferon-alpha (IFN- $\alpha$ ) has been used as adjuvant therapy in pediatric patients with recurrent respiratory papillomatosis (RRP). However, its efficacy in adults needs to be validated. Since 2002, Samsung Medical Center's guidelines have mandated regular injection of IFN- $\alpha$  in patients with RRP to prevent recurrence. To evaluate these guidelines, patient data were investigated.

**Methods:** Five patients diagnosed as having RRP by bronchoscopy and histopathology were included. After initial bronchoscopic intervention, including laser cauterization, all patients received subcutaneous injection of 6 million units of IFN- $\alpha$  every 2 months. Further bronchoscopic intervention was carried out as needed. Patients were regularly evaluated using bronchoscopy or computed tomography.

**Results:** The median age of the patients was 44 years (range 13~68), and the median duration of papillomatosis was 31 years (range 1~45). Three and two patients had juvenile-onset and adult-onset disease, respectively. Two patients had a history of tracheostomy at the time of diagnosis. The median duration of IFN- $\alpha$  therapy was 56 months (range 12~66). Two patients showed complete remission at 12 and 36 months after IFN- $\alpha$  injection, respectively. The other three patients showed partial remission, and the number of laser therapy sessions was significantly reduced.

**Conclusion:** Intermittent IFN- $\alpha$  injection is effective in patients with long-standing RRP and can reduce the number of laser therapy sessions required in their treatment.

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