Objective: To report the benefits and complications of subcutaneous interferon alfa-2a therapy for hemangiomas in children.

Design: Prospective nonrandomized trial.

Setting: Tertiary care pediatric referral center.

Patients: Twenty-four pediatric patients diagnosed with massive or life-threatening hemangiomas.

Interventions: Each patient received daily subcutaneous injections of interferon alfa-2a to a target dose of 3 million U/m² of body surface area for a minimum of 4 months. Nineteen patients completed therapy and have received adequate follow-up.

Main Outcome Measures: Clinical and radiographic comparisons before, during, and after therapy. Reduction in hemangioma size was graded as complete (>90%), substantial (50%-80%), intermediate (20%-40%), or no response (<10%).

Results: Mean age at institution of therapy was 9.6 months, and mean duration of treatment was 10.2 months. Most patients (70%) had not received prior therapy. Responses were as follows: complete, 8 patients (42%); substantial, 3 patients (16%); intermediate, 5 patients (26%); and no response, 3 patients (16%) (n = 19). During therapy, 5 patients (26%) developed neurological abnormalities: 3 had an unsteady gait, and 2 had fine motor deficits. Only 1 of these 5 patients required premature termination from the study, and the neurological abnormalities in all 5 patients resolved after treatment was discontinued. Two of the 4 patients with neurological findings who completed therapy demonstrated complete resolution of their hemangiomas. Patients who developed neurological abnormalities began interferon alfa-2a therapy at an earlier age (4.7 months) than patients without neurological difficulties (aged 11.1 months). The mean time from initiation of therapy to the appearance of neurological complications was 4.8 months.

Conclusions: In pediatric patients with massive or life-threatening hemangiomas, interferon alfa-2a therapy is an effective treatment option. However, neurological evaluation before and during therapy with interferon alfa-2a should be performed owing to a significant incidence of neurological abnormalities (28%). Although all children with neurological findings demonstrated neurological recovery after discontinuation of therapy, we have changed our protocol and now more gradually increase the dosage of interferon alfa-2a up to 3 million U/m² per day. The effect of this modification on the development of neurological abnormalities has not yet been determined.


Hemangiomas are the most common head and neck tumors diagnosed in pediatric patients, affecting nearly 10% of white children and 22% of premature infants. These vascular lesions preferentially affect girls by a 3:1 margin. Initially appearing as an erythematous macular region, hemangiomas enter a proliferative phase and may grow to a relatively large size. After reaching a growth plateau in early childhood, spontaneous regression is the rule, with 50% of lesions resolving by 5 years of age and 70% by 7 years of age. Because most hemangiomas are small, or asymptomatic, treatment is usually not required. However, 5% to 10% of affected children develop cosmetically deforming, functionally impairing, or life-threatening hemangiomas that mandate intervention. Two nonsurgical treatment modalities have been favored, with varying success: high-dose corticosteroid therapy and interferon therapy. Prednisone therapy has been found to be effective in up to 30% of children at dosages of 2 to 4 mg/kg per day; and some response has been reported in an additional 40%. 

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PATIENTS AND METHODS

Twenty-four patients with severe cervicofacial hemangiomas were enrolled in a prospective study to evaluate treatment response to daily subcutaneous injections of interferon alfa-2a. Hemangiomas were diagnosed by physical examination, growth characteristics, and radiographic evaluation, and defined as severe if they were disfiguring, massive in size, compromising the aerodigestive tract, or otherwise life-threatening (eg, Kassabach-Merritt syndrome). Parents were counseled extensively on the risks of interferon alfa-2a therapy, and informed consent was obtained in all cases. The study was performed with the approval of the University of Iowa Institutional Review Board, Iowa City.

Pretreatment evaluation included a complete history, physical examination, and laboratory analysis (complete blood cell count with differential cell count, liver function tests, and determination of serum urea nitrogen and creatinine levels). Photographic and radiographic (computed tomography or magnetic resonance imaging) evaluations were made both before and after treatment. Initial monitoring included monthly clinic visits with repeated laboratory analysis; if all parameters were stable after 4 months, follow-up evaluations were made at 3-month intervals. Interval radiographic evaluation was obtained every 6 to 9 months. Nightly injections were administered at home, initially with nursing supervision, at a dose of 1 million U/m2. Dosages were increased incrementally on a weekly basis to 3 million U/m2. Parents were instructed to keep a diary to monitor for potential adverse effects. In light of the neurological toxic effects noted in some patients enrolled early in the study, interferon alfa-2a doses are now increased on a monthly basis requiring 3 to 4 months to achieve the target dose.

Response to therapy was assessed by physical examination with photographic documentation, radiographic studies, and/or endoscopic examination. Reduction in hemangioma size was graded (in increments of 10%) as complete (≥90%), substantial (50%-80%), intermediate (20%-40%), or no response (≤10%). (Even with “complete” involution, residual fibroadipose tissue and redundant skin remain; therefore, the term complete is in reference to the volume of the hemangioma mass.) If no response to treatment was noted during a 4-month interval of continuous therapy, treatment was discontinued by tapering the dosage of the therapy over a 1-month period. Patients were followed up after treatment to monitor for hemangioma regrowth. Statistical analysis was performed with the SAS statistical program (SAS Inc, Cary, NC) using the paired Student t test, the t correlation test, and the Fisher exact test.

In an attempt to improve outcome and minimize adverse effects of corticosteroid use, other treatments have been sought, with interferon alfa-2a receiving a great deal of recent interest. In 1989, White et al reported the successful use of interferon alfa-2a in the treatment of a child with pulmonary hemangiomatosis. Indications for interferon alfa-2a therapy have since expanded to include hemangiomas that are cosmetically or functionally deforming, of massive size, or life threatening (eg, airway compromise or consumptive coagulopathy). Interferon alfa-2a and interferon alfa-2b appear to be equally effective.

Bauman et al reported our initial experience with interferon alfa-2a for the treatment of massive or life-threatening hemangiomas. Six of 9 patients who received at least 3 months of therapy demonstrated a significant reduction in hemangioma size. Four of the 6 patients had a complete response (>90%), and 2 had a partial response (50%-80%). One patient developed irritability after 1 week of therapy and was withdrawn at parental request; no other significant complications were noted. This expanded study describes our experience with 24 children over a 6-year period. Nineteen patients were available for long-term follow-up. Reversible neurological toxic effects, consisting primarily of fine motor and gait abnormalities, were observed in a significant number of patients. Alterations in our treatment program include performing frequent neurological evaluations and modifying the interferon alfa-2a dosage schedule.

RESULTS

Nineteen of 24 patients enrolled in this study had an adequate course of therapy (minimum, 4 months) and are the subjects of this report. Of the 5 patients not included in the study, 3 have been receiving therapy for less than 3 months, 1 was withdrawn at the parents’ request after 1 month of therapy, and 1 was excluded when angiography suggested that the lesion was an arteriovenous malformation, not a hemangioma. In the study group, the mean age at presentation and initiation of therapy was 2 weeks and 10 months, respectively. Most hemangiomas (61%) were present at birth, appearing as erythematous macular regions. Thirteen patients were female, and 6 were male. Seventeen of the 19 study patients were white, 1 was Hispanic, and 1 was African American. The mean duration of therapy for the 16 patients who have completed interferon alfa-2a therapy was 16 months (range, 6-26 months). The 3 remaining patients are still receiving interferon alfa-2a and have received 9, 10, and 15 months of treatment at the time this article was written.

The most common presenting symptoms were facial disfigurement (84%), airway obstruction (42%), and failure to thrive (21%).

<table>
<thead>
<tr>
<th>Presenting Symptoms</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial disfigurement</td>
<td>16</td>
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<tr>
<td>Airway obstruction</td>
<td>8</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>7</td>
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<tr>
<td>Pain/irritability</td>
<td>3</td>
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<tr>
<td>Dysphagia</td>
<td>3</td>
</tr>
<tr>
<td>Visual deficit</td>
<td>2</td>
</tr>
<tr>
<td>Infection</td>
<td>2</td>
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<tr>
<td>Bleeding/anemia</td>
<td>2</td>
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</tbody>
</table>

No patient presented with thrombocytopenia. Five patients (26%) required a tracheotomy for airway stabilization before starting therapy with interferon alfa-2a. Physical and radiographic evaluation revealed the most common site of hemangiomas to be the cheek/parotid re-
region (53%). Involvement of the cervical region (42%) and airway (42%) was also frequently noted.

<table>
<thead>
<tr>
<th>Location of the Hemangiomas</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheek/parotid region</td>
<td>10</td>
</tr>
<tr>
<td>Neck</td>
<td>8</td>
</tr>
<tr>
<td>Airway</td>
<td>8</td>
</tr>
<tr>
<td>Nasal cavity</td>
<td>3</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>4</td>
</tr>
<tr>
<td>Larynx/subglottis</td>
<td>4</td>
</tr>
<tr>
<td>Nose/orbits</td>
<td>5</td>
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<tr>
<td>Pinna/external auditory canal</td>
<td>4</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>1</td>
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<tr>
<td>Scalp</td>
<td>1</td>
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Six patients had received alternative therapy before starting interferon alfa-2a therapy, including treatment with systemic corticosteroids (4 patients), intraleisonal steroids and external laser ablation (1 patient), and incomplete surgical excision (1 patient).

Eight patients (42%) demonstrated a complete response to interferon alfa-2a, and 3 patients (16%) had a substantial response. Overall, 58% of patients demonstrated a greater than 50% reduction in hemangioma size. Five patients (26%) showed only an intermediate response, and 3 patients had no response to therapy. In the 15 patients who had some response to therapy, the mean time to onset of involution was 6 weeks (range, 4-24 weeks). The mean duration of therapy in the 13 responders who are no longer taking the medication was 16 months.

**Figure 1** represents the long-term follow-up of a 4-year-old patient with a parotid hemangioma who demonstrated a complete response after 1 year of interferon alfa-2a therapy. Scar revision and laser resurfacing for the residual fibrofatty tissue have enhanced her cosmetic appearance. Similarly, **Figure 2** shows the dramatic response of a parotid hemangioma in a 3-month-old who has received interferon alfa-2a therapy for 16 months. In both patients, involution began after 6 weeks of therapy. **Figure 3** demonstrates complete resolution of an obliterating subglottic hemangioma, which allowed decannulation after 9 months of interferon alfa-2a therapy.

Of patients with hemangiomas of the cheek/parotid region, 73% demonstrated a greater than 50% response to interferon alfa-2a therapy, compared with 38% of patients with other sites of involvement. When cervical and parotid lesions were considered together, the combined complete and significant response rate remained essentially unchanged at 70%, but was only 33% for other sites. Neither comparison was statistically significant ($P = .18$).

Similar analysis of airway lesions showed only a 50% significant or complete response rate, although 3 of 4 patients with only subglottic hemangiomas had complete responses to therapy and underwent decannulation. Despite the institution of limited carbon dioxide laser therapy in these patients with subglottic hemangiomas, the dramatic response to therapy was temporarily related to interferon alfa-2a therapy. Age at initiation of therapy was associated with response to therapy, as patients who demonstrated any response to therapy (complete, significant, or intermediate) were significantly younger than nonresponders (6.8 months vs 25.7 months, respectively; $P = .001$). No correlation was found between success with interferon alfa-2a therapy and sex or race.

All patients experienced mild pyrexia (38°C-39°C) during the first 4 to 6 weeks of therapy and were treated with acetaminophen. No patients discontinued interferon alfa-2a therapy because of hyperpyrexia. Other self-limiting complications were mild transient elevations in liver function test results and anorexia, although several patients also had mild elevations in liver function test results (42%), mild anemia (26%), and mild thrombocytosis (26%) prior to treatment. During interferon alfa-2a therapy, hemoglobin levels returned to normal in all patients with anemia; no significant changes were seen in patients with elevated liver function test results or platelet counts.

Five patients (26%) developed fine motor and gait abnormalities during interferon alfa-2a therapy (Table). Three patients were noted to have an unsteady gait and delayed walking and crawling, and 2 patients developed delayed fine motor control of the hands. The mean time at presentation of these neurological changes from initiation of the therapy was 4.8 months (range, 3-8 months). Four patients finished the therapy, and in all of them, the symptoms resolved completely after the therapy was discontinued. Younger age at onset of therapy appeared to be a potential risk factor for neurological changes (age 4.7 months vs 11.1 months, respectively; $P = .08$). A significant correlation was found between response to therapy and the development of neurological complications: as response lessened, the likelihood of neurological findings increased ($\tau = -0.3617; P = .05$).

**COMMENT**

The diagnosis and treatment of massive or life-threatening hemangiomas in children can be challenging. In the absence of the typical cutaneous findings on physical examination (Figure 2), radiographic imaging can be used to confirm the diagnosis and to determine the extent of involvement. Magnetic resonance imaging is more accurate than computed tomography to differentiate vascular malformations from hemangiomas, which are characterized by small-diameter, high-volume flow voids with enhancement of the surrounding soft tissue on gadolinium $T_1$-weighted images. However, in light of the distinctly different treatments for the 2 vascular lesions, an arteriogram also may be required, especially if embolization therapy is contemplated.

In our study, 1 patient failed to demonstrate any degree of spontaneous involution, even by 10 years of age, and no response to interferon alfa-2a was seen. Subsequent angiographic evaluation in this patient confirmed the lesion to be a venous vascular malformation. None of our patients presented with thrombocytopenia or Kassabach-Merritt syndrome; however, either size or location of the hemangiomas caused significant morbidity. In addition to the obvious cosmetic deformity of primary concern to the parents, airway protection, dysphagia, and failure to thrive were important factors in mandating treatment. In light of the generally poorer response to high doses of corticosteroids and their associated morbidity, interferon...
alfa-2a therapy has been our preferred method of treatment. Initial reports have confirmed the short-term efficacy of interferon alfa-2a therapy, although, to our knowledge, long-term efficacy and morbidity have not been studied.

Adverse effects from prolonged high-dose corticosteroid therapy or intralesional steroid injections are well documented. They include growth retardation, failure to thrive, irritability, immunosuppression, adrenal suppression, edema, and glucose intolerance. Enjolras et al noted severe growth retardation in 13 of 25 children with hemangiomas who were receiving prolonged high-dose corticosteroid therapy (2-3 mg/kg of prednisone or prednisolone). No mention of adverse long-term growth sequelae was made in their report. Also, 1 patient developed a duodenal ulcer and treatment was discontinued.

Figure 1. Long-term follow-up photograph of a patient from our early experience of treatment with interferon alfa-2a. She presented with a massive facial/parotid hemangioma at the age of 2 months (left). Note the irregular nodular surface indicative of involvement of the superficial dermis. After the initiation of interferon alfa-2a therapy, involution began at the age of 3 months, and after 15 months of therapy, marked improvement is seen (right).

Figure 2. Pretreatment (left) and posttreatment (right) photographs of a patient with a massive facial/parotid hemangioma, which presented at birth and grew rapidly by the age of 3 months (left). Involution began after 3 months of interferon alfa-2a therapy, and the patient received a total of 16 months of therapy. The posttreatment photograph taken when the patient was 2 years old shows an excellent result (right).
Sloan et al\textsuperscript{17} reported a 10\% incidence of a cushingoid appearance in patients receiving intralesional steroid therapy for cutaneous hemangiomas, with or without concomitant oral corticosteroid therapy. Prolonged corticosteroid therapy in children with inflammatory bowel disease was found to be associated with osteopenia in almost 50\% of the patients treated.\textsuperscript{18}

To our knowledge, this series represents the largest reported cohort of patients with hemangiomas treated with interferon alfa-2a. Results confirm that interferon alfa-2a therapy is more effective than corticosteroid therapy for massive or life-threatening lesions, with response rates of 58\% vs reported rates of 30\% for corticosteroid therapy.\textsuperscript{5-19} Of the 4 patients in this series in whom initial corticosteroid therapy failed, 2 attained a complete response and 2 an intermediate response with interferon alfa-2a therapy. No rebound growth of the hemangiomas was noted as the dosage of interferon alfa-2a was tapered and stopped in either responders or nonresponders.

Location in the cheek/parotid region appeared to be the best prognostic indicator of response, as twice as many patients with lesions of the lateral cervicofacial region responded well to therapy. This observation is in agreement with the results reported by MacArthur et al,\textsuperscript{9} but differs from those of Blei et al.\textsuperscript{10} In Blei and colleagues’ study, 3 of the 7 patients with parotid hemangiomas in whom interferon alfa-2a therapy failed received less than 3 months of therapy, and it is possible that this short duration of treatment accounted for the minimal response that was observed. We hypothesize that the increased blood flow and high metabolic activity of the parotid gland enhances the delivery of interferon alfa-2a to the hemangioma and possibly explains our findings of improved resolution.

Interferon alfa-2a therapy also appears to be more effective when it is initiated at an early age. Although our group of nonresponders was small (n = 3), these patients were significantly older than those who responded to therapy, a difference that may be explained by the natural course of hemangiomas. Since inhibition of endothelial cell growth is the presumed mechanism of interferon alfa-2a’s effect, the most dramatic response would be expected during the early proliferative phase of the hemangioma. Because of the small number of patients in each response group, no age-related differences in degree of response could be determined, and a multi-institutional study would be required to address this issue.

Lack of hemangioma response to interferon alfa-2a therapy may reflect the development of binding or neutralizing antibodies. Idéo et al\textsuperscript{20} reported that these antibodies developed in 27\% of patients who received interferon alfa-2a for chronic hepatitis, and in another study of more than 250 patients treated with interferon alfa-2a, interferon alfa-2b, or lymphoblastoid interferon, Antonelli et al\textsuperscript{21} found the development of neutralizing antibodies in 20.9\%, 6.9\%, and 1.2\% of patients, respectively. In both the interferon alfa-2a and the interferon alfa-2b treatment groups, this finding was associated with reduced efficacy of therapy. Antonelli et al\textsuperscript{22} also described 45 patients receiving interferon alfa-2a therapy who had a relapse of their chronic hepatitis. There was a significant increase in neutralizing (64\%) and binding (69\%) antibodies in those relapsing patients compared with controls, thereby implicating the formation of interferon antibodies with the lack of therapeutic effect. Further studies are needed to determine whether antibody for-

\begin{table}[h]
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\begin{tabular}{|c|c|c|}
\hline
Complications & No. of Patients &  \\
\hline
Pyrexia (38°C-39°C) & 0 & 19 \\
Elevated liver function test results & 9 & 3 \\
Lactate dehydrogenase & 9 & 4 \\
Aspartate aminotransferase & 7 & 5 \\
Alkaline phosphatase & 7 & 1 \\
Neurologic (motor) dysfunction & 0 & 5 \\
Anorexia & 7 & 1 \\
Anemia & 5 & 0 \\
Thrombocytosis & 5 & 0 \\
\hline
\end{tabular}
\caption{Complications During Interferon Alfa-2a Therapy in 19 Patients}
\end{table}
mation has an impact on either initial response to therapy or treatment duration in patients with hemangiomas.

Adverse effects of interferon alfa-2a therapy are well documented and include constitutional symptoms (eg, fever, malaise, and fatigue), elevated liver enzyme levels, nausea, renal failure, and bone marrow suppression, although toxic reactions have been reported in all organ systems. As expected, all our patients did have constitutional symptoms. However, during and after therapy, further elevations in liver enzyme levels and evidence of hematological abnormalities were not noted. In fact, during interferon alfa-2a therapy, the results of liver function tests normalized in more than 50% of our patients and anemia and thrombocytosis resolved in all of them (Table).

Although uptake of interferons in the central nervous system has not been demonstrated, neurological toxic effects have been reported in up to 34% of adult patients with cancer treated with interferon alfa-2a at dosages of 5 to 18 million U/m² per day. These central nervous system effects are presumably due to induced toxic proteins, such as cytokines (eg, interleukin 1). Kemeny et al reported that of 38 patients receiving a combination of interferon alfa-2a and fluorouracil for advanced colorectal cancer, 34% developed gait abnormalities and 16% displayed memory disturbances. Pazdur et al noted severe ataxia and gait abnormalities in 1 of 49 patients on the same treatment regimen and grade 1 neurotoxic effects (not defined) in 2. In both studies, the gait abnormalities resolved with cessation of interferon alfa-2a therapy. In contrast, Fossa et al reported no neurotoxic effects in 23 patients with renal cell carcinoma treated with 18 million U/m² of interferon alfa-2a 3 times a week and oral prednisone (10-20 mg/d).

Bauher et al described a patient undergoing interferon alfa-2a therapy (5 million U/m² per day) for hairy cell leukemia who developed progressive bilateral ocular motor nerve paralysis after 3 months of treatment. Within weeks of discontinuation of interferon alfa-2a therapy, the paralysis completely resolved. Peripheral nervous system toxic effects (paresthesia or numbness) were also reported by Jones and Itri in up to 7% of more than 1000 patients receiving interferon alfa-2a therapy. Like the central nervous system toxic effects, the paresthesias and numbness resolved after discontinuation of therapy.

Neurological complications in patients with hemangiomas treated with interferon were first reported by Chang et al. They described a patient who had delayed gross motor skills that were thought to be due to interferon alfa-2b therapy (3 million U/m² per day). These motor deficits resolved after treatment was discontinued, with no permanent sequelae. Barlow et al recently described 5 patients with spastic diplegia among a cohort of 26 infants treated with interferon alfa-2a for hemangiomas. Two patients developed gait, posture, and fine motor deficits after 4 to 6 months of therapy. The interferon therapy was discontinued, and their symptoms resolved within 3 months. Three patients had persistent neurological deficits, which included abnormalities of gait and speech. In 2 of these children who were treated from 1 to 9 months of age, the neurological findings did not appear until they were 17 months old. The third patient with persistent neurological dysfunction had received a prolonged course of therapy (21 months) before her symptoms appeared.

This study is the second (to our knowledge) to document neurological complications in infants and children receiving relatively low-dose interferon alfa-2a for hemangiomas. As with the central and peripheral neurological signs reported previously, gait and fine motor abnormalities resolved within weeks of the discontinuation of therapy. Interestingly, neurological abnormalities have not been reported in patients receiving comparable doses for viral hepatitis, a discrepancy that may be the result of age differences. Although the mechanism of interferon alfa-2a–induced neurotoxic effects is not known, perhaps younger patients are at greater risk for gait and fine motor abnormalities because their neurological systems are still developing.

The finding of a negative correlation between treatment response and the presence of neurological complications is puzzling. No differences in treatment length or age were demonstrated, and this “effect” may be secondary to the small number of patients in each treatment group. To better monitor children during interferon alfa-2a therapy, we have adjusted our protocol and gradually increase drug dosage from 1 million to 3 million U/m² per day over 3 to 4 months. Further studies will be required to determine whether this modification reduces the neurological morbidity.

Interferon alfa-2a therapy is an important treatment option for children with life-threatening or cosmetically deforming head and neck hemangiomas. Eighty-four percent of the patients in our study demonstrated a response to interferon alfa-2a therapy, and 42% had complete resolution of their hemangioma. All patients except 1 were able to complete a full course of therapy. Twenty-six percent of patients developed reversible fine or gross motor delay that resolved at the completion of therapy. No permanent sequelae have been documented in these children. Neurological changes were related to the early initiation of therapy (before the patients were 10 months old). We now recommend pretreatment and continual neurological evaluation with appropriate parental counseling if interferon alfa-2a therapy is being considered in children younger than 1 year. We also recommend gradual dose increments (1 million U/mo) to reach the target dose of 3 million U/m² per day.

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