Interferons and Their Application in Lung Diseases

To the Editor:

We enjoyed the comprehensive review on the potential therapeutic applications of interferon (IFN) in pulmonary diseases by Antoniou and associates (January 2003).1 Here, we would like to extend the conditions responsive to IFN treatment to include the Churg-Strauss syndrome (CSS).

The CSS is an uncommon type of eosinophilic granulomatous inflammation with associated vascular necrosis accompanied by marked eosinophilia, raised IgE serum concentrations, and usually severe corticosteroid-dependent perennial asthma.2 In 1997, we treated a 31-year-old woman with a histologically proven CSS resistant to first-line therapy. Administration of IFN-γ (50 μg) lead to a substantial clinical improvement allowing a low-dose steroid maintenance therapy.3 During the past 3 years, we have offered IFN treatment to four additional patients with histologically confirmed CSS who were either resistant to standard therapy (oral corticosteroid alone or in combination with immunsuppressants) or suffered from severe drug-related side effects (Table 1).

The patients were treated with 9 μg IFN-αcon (equivalent to 3 million units of IFN-α2b) administered subcutaneously thrice weekly. In all patients, IFN-α induced a significant clinical improvement with respect to clinically relevant parameters of the disease (asthma, rhinitis, sinusitis, hypereosinophilia) with partial (patients KV and BG) and complete remissions (patients KV and BK). In patient KV, both the symptoms of the hemorraghic cystitis and the Cushing syndrome (weight reduction of 19 kg) disappeared. Also, the peripheral polyneuropathy in patient KV continues to improve since initiation of therapy. The above improvements were achieved despite tapering of oral steroids in all patients. In two patients (patients KV and BK), corticoid treatment could be discontinued. Side effects occurring 2 to 12 h after steroids in all patients. In two patients (patients KV and BK), corticoid treatment could be discontinued. Side effects occurring 2 to 12 h after treatment could be discontinued. Side effects occurring 2 to 12 h after injection included arthralgia, nausea, malaise, and fever, but were transient and decreased within 3 to 4 weeks. One patient (patient UG) acquired a hyperthyroidism 5 months after initiation of IFN therapy.

Our data are supported by a total of six patients who have also responded to IFN. Tatsis et al4 studied the effect of IFN-α (7.5 to 63 million U/wk) on four patients with CSS. Treatment led to a remission of the disease in all patients and a substantial reduction of the prednisolone requirement in two patients who had attained incomplete remission with cyclophosphamide or methotrexate. In one patient, stabilization of the condition was achieved. Interestingly, another sustained remission was achieved after treatment for 1 year. Lesens et al5 reported a case of severe CSS resistant to standard treatment with mediastinal eosinophilic lymphadenopathy, which showed significant clinical improvement after IFN-α2b was initiated. A beneficial response to treatment with interferon-α2b was also observed in a patient with prominent skin involvement.6 Taken together, the data summarized above suggest that CSS may be another pulmonary disease entity responding to treatment with IFN.

Claus Kroegel, MD, PhD, FCCP
Bettina Mock, MD
Angelika Reissig, MD
Friedrich-Schiller-University
Jena, Germany

to the Editor:

We thank Kroegel and colleagues for their interest in our recent review1 on interferons and their application in the diseases of the lung. There are, indeed, a few case reports indicating the beneficial role of interferon-α and interferon-γ in various rare interstitial lung diseases, such as idiopathic hypereosinophilic syndrome2–4 and the Churg-Strauss syndrome.5–7 However, given

Table 1—Effect of IFN-α Treatment on the Clinical Course of the Four Patients With CSS

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, yr/Sex</th>
<th>Duration of CSS, yr</th>
<th>Symptoms at Admission</th>
<th>IFN-αcon Treatment Duration, mo</th>
<th>Clinical Course Under IFN Therapy</th>
<th>Required Oral Steroid-Dose Prior to IFN Therapy/Current Dose, mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>KV</td>
<td>59/female</td>
<td>4</td>
<td>Asthma, rhinitis, sinusitis, polyneuritis</td>
<td>42</td>
<td>Complete clinical remission</td>
<td>25 to 50/none (off steroids for 32 mo)</td>
</tr>
<tr>
<td>BK</td>
<td>30/male</td>
<td>11</td>
<td>Asthma, hemorrhagic cystitis, sinusitis, rhinitis, Cushing syndrome</td>
<td>31</td>
<td>Complete clinical remission</td>
<td>12 to 25/none (off steroids for 18 mo)</td>
</tr>
<tr>
<td>BG</td>
<td>39/female</td>
<td>5</td>
<td>Asthma, sinusitis, rhinitis, polyneuritis, heart involvement (Löffler endocarditis)</td>
<td>17</td>
<td>Partial remission</td>
<td>40 to 20/10</td>
</tr>
<tr>
<td>UG</td>
<td>51/female</td>
<td>9</td>
<td>Asthma, rhinitis, sinusitis</td>
<td>15</td>
<td>Partial remission</td>
<td>15 to 30/4</td>
</tr>
</tbody>
</table>

REFERENCES

the rarity and the course variability of these diseases, multicenter, comparative trials are needed in order to verify these case reports.

Demostenes Bourou, MD, FCCP
Medical School University of Thrace
Alexandroupolis, Greece

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Correspondence to: Demostenes Bourou, MD, FCCP, Department of Pneumonology, Medical School University of Thrace, Alexandroupolis 68100, Greece; e-mail: bourou@med.duth.gr

REFERENCES


Mice Are Resistant to the Induction of a Pleurodesis

To the Editor:

Our group has shown that transforming growth factor (TGF-β2) produces excellent pleurodesis when administered intrapleurally in rabbits and sheep.1–2 It induces pleurodesis faster than talc, and the pleural fluid that is produced after its intrapleural administration is less inflammatory than that produced after the administration of talc or doxycycline. Hence, pleurodesis caused by TGF-β2 may be effective but less painful and safer when compared to the pleurodesis caused by sclerosing agents currently used in clinical practice.

However, the mechanisms of pleurodesis induced by TGF-β2 as well as by conventional agents are largely unknown. In order to expand our capabilities of examining the molecular mechanisms of pleurodesis induced by TGF-β2, or other agents, we attempted to create a mouse model of pleurodesis. A mouse model of pleurodesis would be superior to the rabbit or sheep models for the following reasons: (1) the availability of knockout mouse strains would allow one to investigate the mechanism of pleurodesis in more depth, (2) there are many more commercial reagents specific for mice proteins than for sheep or rabbit proteins, and (3) mice are much less expensive.

TGF-β2 was injected intrapleurally in ICR mice at doses 0.5 to 1.360 μg/kg (Table 1). Talc, 4g/kg, and doxycycline, 20 to 100 mg/kg, were also injected. During the first experiments, we combined the “effective” agent with India ink to verify successful intrapleural injection. Since the injection rate was successful in > 95%, we performed the next experiments without ink to eliminate the possibility that the ink reduced the TGF-β2 activity. Since epidermal growth factor (EGF) is believed to amplify the fibrosing effect of TGF-β2, we injected some mice with the combination of the two growth factors and with EGF alone. Mice were killed at the 14th day after the injection, and the thorax was examined for pleurodesis. A scale from 1 to 8 was used to evaluate the degree of pleurodesis: 1 = no adhesions, 2 = rare adhesions with no symphysis, 3 = a few scattered adhesions with no symphysis, 4 = many adhesions with no symphysis, 5 = many adhesions with symphysis involving < 5% of the thoracic cavity, 6 = many adhesions with symphysis involving 5 to 25% of the thoracic cavity, 7 = many adhesions with symphysis involving 25 to 50% of the thoracic cavity, and 8 = many adhesions with symphysis involving > 50% of the thoracic cavity.

TGF-β2 did not induce pleurodesis, even when administered at doses 130 times higher than the dose that induced intensive pleural fibrinosis in rabbits. No more than few scattered pleural adhesions were observed. Furthermore, clinically significant pleurodesis was not observed in any of the mice receiving talc or doxycycline, even when they were administered in doses 10 times higher than those that induce pleurodesis in rabbits. Because different mouse strain show different susceptibility for pulmonary fibrosis and C57/Bl-6 mice have been shown to be particularly susceptible to pulmonary fibrosis,1 we injected the TGF-β2 in eight C57/Bl-6 mice to rule out the possibility that the failure of TGF-β2 to produce pleurodesis was due to the mouse strain we initially used (ICR mice). As it is shown in Table 1, TGF-β2 also failed to induce significant pleurodesis in these mice.

We conclude from this series of experiments that TGF-β2, doxycycline, and talc do not induce pleurodesis when administered intrapleurally in mice at relatively high doses. The explanation for the refractoriness of the mouse for the induction of a pleurodesis is unknown.

Ioannis Kalomenidis, MD
Athens Medical School
Athens, Greece

Kirk Lane, PhD
Timothy S. Blackwell, MD, FCCP
Yubiao Guo, MD
Richard W. Light, MD, FCCP
Vanderbilt University
Nashville, TN

Table 1—Pleurodesis Score in Different Treatment Groups*

<table>
<thead>
<tr>
<th>Injected Agents</th>
<th>No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ink</td>
<td>10</td>
<td>8</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β2 0.8 μg/kg plus ink</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β2 2.5 μg/kg plus ink</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β2 7.5 μg/kg plus ink</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β2 16 μg/kg</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TGF-β2 22.5 μg/kg</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TGF-β2 67.5 μg/kg</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β2 202.5 μg/kg plus ink</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TGF-β2 312.5 μg/kg</td>
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<td>2</td>
<td>2</td>
<td></td>
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<tr>
<td>TGF-β2 600 μg/kg</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TGF-β2 1360 μg/kg</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TGF-β2 10 μg/kg†</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td></td>
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<tr>
<td>TGF-β2 250 μg/kg†</td>
<td>4</td>
<td>3</td>
<td>1</td>
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<td></td>
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<tr>
<td>TGF-β 510 μg/kg plus EGF 4 μg/kg</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β 510 μg/kg plus EGF 8 μg/kg</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
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<tr>
<td>EGF 8 μg/kg</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td></td>
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<tr>
<td>Doxycycline 10 mg/kg plus ink</td>
<td>3</td>
<td>2</td>
<td>1</td>
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<td></td>
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<tr>
<td>Doxycycline 20 mg/kg plus ink</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Doxycycline 100 mg/kg plus ink</td>
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<td>1</td>
<td>1</td>
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<td></td>
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<tr>
<td>Tale 4 g/kg</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

†ICR mouse unless otherwise indicated.

C57/Bl-6 mice.

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