Interferon α-2b Injection – Still a Viable Option?

Andrew McCullough, MD
Professor of Surgery/Division of Urology
Albany Medical College
Albany, NY
## Relevant Disclosure

Under Accreditation Council for Continuing Medical Education guidelines disclosure must be made regarding financial relationships with commercial interests within the last 12 months.

### Andrew McCullough, MD

<table>
<thead>
<tr>
<th>Company</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repros</td>
<td>Consultant, Stock</td>
</tr>
<tr>
<td>Endo (Auxillium)</td>
<td>Research Grant, Consultant, Speaker</td>
</tr>
<tr>
<td>Pfizer</td>
<td>DSMB, Stock</td>
</tr>
<tr>
<td>Abbvie</td>
<td>Research Grant</td>
</tr>
<tr>
<td>Coloplast</td>
<td>Research Grant</td>
</tr>
<tr>
<td>AMS</td>
<td>Research Grant</td>
</tr>
<tr>
<td>Astellas</td>
<td>Research Grant</td>
</tr>
</tbody>
</table>
Interferon Alpha 2b

- IFN-2b molecule is a glycoprotein consisting of 166 amino acids
- Discovered in 1957
- Based on crystal structure that is mediated by zinc dimer, each monomer of IFN-2b consists of five alpha helices (called helix A to E)
- The most oncological indication of hIFN-α2b includes
  - hairy cell leukemia
  - melanoma,
  - follicular lymphoma
  - renal cell carcinoma
  - AIDS-related Kaposi’s sarcoma
  - chronic myelogenous leukemia
- IFN-α-2B has only a 2-hour half-life, which may limit its ongoing benefit on suppression of collagen synthesis or stimulation of collagenase activity.
Antiproliferative and Apoptotic pathway
Dosing

- **Hairy Cell Leukemia**
  - 2 million U/sq.meter IM/SC 3 times/wk for up to 6 mo

- **Malignant Melanoma**
  - Induction 20 million U/sq.meter IV over 20 min, 5 days/wk for 4 wk
  - Maintenance dose: 10 million U/sq.meter SC 3 times/wk for 48 wk

- **Follicular Lymphoma**
  - 5 million U 3 times/week for up to 18 mo

- **Condylomata**
  - 1 million U injected into each lesion 3 times/week for 3 week
  - Repeat 12-16 wk after initial treatment

- **Aids Koposki Sarcoma**
  - 30 million U/sq.meter IM/SC 3 times/wk for 16 wk

- **Chronic Hep C**
  - 3 million U IM/SC 3 times/wk for 16 wk
Hairy Cell Leukemia

- The route of administration for hairy cell leukemia is subcutaneous and the recommended dose is 2 million U/m$^2$ three times weekly for 12 months.
- The IFN therapy was generally well tolerated, but 24 month evaluation showed mild toxicity in about 76% of the patients.
- There was a study which reported unexpected high incidence of second neoplasm in patients after IFN-α2b treatments with the same dose for 12 to 18 months of therapy.
- There were 13 patients from 69 who developed second neoplasm.

Interferons in Dermatology Show promise!

Short-term keloid treatment in vivo with human interferon alfa-2b results in a selective and persistent normalization of keloidal fibroblast collagen, glycosaminoglycan, and collagenase production in vitro

Brian Berman, MD, PhD, and Matthew R. Duncan, PhD Davis and Martinez, California

Journal of the American Academy of Dermatology
1989
REGULATION OF THE PROLIFERATION AND BIOSYNTHETIC ACTIVITIES OF CULTURED HUMAN PEYRONIE'S DISEASE FIBROBLASTS BY INTERFERONS-ALPHA, -BETA AND -GAMMA,

1. Inhibits Fibroblast Proliferation

2. Did not increase profibrotic glycosaminoglycans

3. Decreased Collagen Production

4. Increased Collagenase production

Table I. Collagen production during a 24-hour period by confluent fibroblasts cultured with or without the indicated concentrations of IFNs was assessed by $^3$H-proline incorporation into collagenous protein.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Interferon concentration (U/ml)</th>
<th>$^3$H-collagen (DPM±SD)/10^5 cells</th>
<th>Collagen production (percent control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0</td>
<td>196±7.0</td>
<td>100</td>
</tr>
<tr>
<td>IFN-α2</td>
<td>10</td>
<td>176.8±6.0</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>$10^3$</td>
<td>137.5±2.0</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>$10^4$</td>
<td>110.8±5.1</td>
<td>56</td>
</tr>
<tr>
<td>IFN-β</td>
<td>10</td>
<td>188.5±15.4</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>$10^3$</td>
<td>111.6±11.0</td>
<td>57</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>10</td>
<td>78.2±6.0</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>$10^3$</td>
<td>89.7±5.1</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>$10^4$</td>
<td>44.6±7.2</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>$10^5$</td>
<td>45.5±4.0</td>
<td>23</td>
</tr>
</tbody>
</table>

Fig. 4. Collagenase activity elaborated into culture media during a 48 hour period by confluent fibroblasts cultured with or without the indicated concentrations of IFNs was assessed, following activation with trypsin, by its ability to solubilize $^3$H-labeled rat (type I) collagen fibrillar gels.
Phase 2 study of Interferon

- 25 men Average age 48
- Duration of Peyronies 26 months
- Average plaque size 1.65 cm; Deviation 17°
- 1 MU weekly for 5 weeks (5 injections /5 Mu)
- Assessed by ultrasound at 1 and 6 months

Results
- Clinical improvement in 1
- Resolution of pain in all
- Measurable decrease in 7, No change in 12 and Increase in 6
- Most beneficial in short duration with no calcification

Local Interferon-Alpha2b Is Not an Effective Treatment in Early-Stage Peyronie’s Disease

- 30 men  Average age 45.2  Duration 7 months
- Early Peyronies average deviation 10°; Plaque size 1 cm and noncalcified
- 3 MU  for 3 weeks (3 injections/9 Mu)
- Ultrasound at 6 months
- Results:
  - 29/30 resolution of pain
  - New plaques in 7
- 8 working days were lost  Myalgias in 65/90 injections

Wegner 1997  European Urology
Local Interferon-Alpha2b Is Not an Effective Treatment in Early-Stage Peyronie's Disease

• “IFN’s do seem to alter the behavior of the treated plaque, but the side effects clearly render them clinically useless and do not allow for a dosage increase or the simultaneous treatment of many sites….”

• … the multi-site onset in 25% of the cases demands a pantunical/pancavernosal approach; local injection therapy ought to be abandoned”

Wegner 1997 European Urology
Intralesion interferon

- 13 men (10 Interferon /3 saline) Average age 56 years
- Duration of Peyronies 2 years
- **1.5 million units 3 x a week for 3 weeks (9 injections/13.5 Mu)**
- Median deviation 50° dorsal, 40° ventral, 45° lateral
- 60% were softer and 30% were smaller
- 20° improvement in curvature measured by penile tracings and photograph after PGE-1 injection
- **Improvement began after the sixth injection and did not change after cessation**
- All on IFN had fevers, chills and myalgias within 1-2 hours of injection and subsided after 2 hours
- Caveats
  - No ultrasound
  - Methods are vague
  - No blind

Judge et al BJU 1997 (79) 40-42
A Pilot Study Demonstrating Clinical Benefit From Intralesional Interferon Alpha 2B in the Treatment of Peyronie’s Disease

- 21 patients mean age 55
- Prospective non randomized
- Plaque measured by caliper; curvature measured by protractor after PGE injection
- 1 MU (in 10 cc) bi-weekly for 6 months (12 injections/12 Mu)

“IFN-α-2B has only a 2-hour half-life, which may limit its ongoing benefit on suppression of collagen synthesis or stimulation of collagenase activity”

Hellstrom: J of Andrology 20(4)1999
Treatment of Peyronie’s disease with local interferon-a 2b

- 23 patients mean age 53 Prospective non randomized
- Peyronies duration 6 months
- 2 MU thrice weekly for 3 weeks (9 injections /18 Mu)
- Eval at 1 and 3 months
- Results:
  - No sig decrease in plaque size
  - Curvature improved in 1 patient
  - 13/19 of patients improved in pain
  - No loss of working days; flu like sx in 2% of injections

“..the outcome of interferon α 2b is unsatisfactory. The drug cannot be recommended for the conservative treatment of Peyronie’s disease”

Brake 2001 87(654-657)BJIU
Interferon and Vitamin D

- 29 men average age 55.8; PD for > 6 months; Curve = 43°
- Plaque size .8 cm
- 4 MU in 10 cc weekly for 10 weeks (10 injections/40 Mu)
- Protractor and PGE-1 injection
- 18/29 (62%) finished (4 unhappy, 4 AE, 3 LTF)
- Results (LOCF)
  - 24% had at least 25% improvement in curvature
  - 100% had “softening” and 6% pain free
  - 34% had “better erections”
  - All had flu like sx

Hellstrom J LA State Med Society 2001
Intralesional Interferon-α-2B Injections for the treatment of Peyronies Disease

- 21 men average age 55.8; PD for 6 months; Curve >15°
- 7 men had placebo (saline) for 6 weeks first 21 had interferon
- 2 MU biweekly in 10 cc saline for 6 weeks (12 injections/24 Mu)
- Results
  - None had improvement with saline
  - 67% had at least 20% improvement in curvature
  - 80% had improvement in pain
  - Plaque size subjectively decreased in 71%

Table 6. Comparative results of the penile duplex Doppler ultrasonography on 21 patients with Peyronie’s disease treated with intralesional interferon

<table>
<thead>
<tr>
<th>Vascular impairment</th>
<th>No. affected</th>
<th>No. improved</th>
<th>No. with no significant improvement</th>
<th>No. worsened</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial insufficiency</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Venous leakage</td>
<td>17</td>
<td>3</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>
The Impact of Intralesional Interferon α-2b Injection Therapy on Penile Hemodynamics in Men with Peyronie’s Disease: Randomized placebo controlled

- 29 (1:1) men average age 55.6; PD for 12 months; Curve >30°
- 5 MU every other week in 10 cc saline vs saline every other week (6 injections/30 Mu)

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Mean PSV, EDV, and RI measurements and P values in each PD group before and after treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 20)</td>
<td>After</td>
</tr>
<tr>
<td>PSV (cm/second)</td>
<td>31.36 ± 1.60</td>
</tr>
<tr>
<td>EDV (cm/second)</td>
<td>5.63 ± 1.31</td>
</tr>
<tr>
<td>RI</td>
<td>0.83 ± 0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Mean pre- and post-treatment PD parameters in the placebo and IFN α-2b-treated patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameters</td>
<td>Placebo (n = 20)</td>
</tr>
<tr>
<td>Curvature (degree)</td>
<td>47.75 ± 2.84</td>
</tr>
<tr>
<td>Plaque size (cm²)</td>
<td>4.60 ± 0.44</td>
</tr>
<tr>
<td>Plaque density (0–3)</td>
<td>2.10 ± 0.20</td>
</tr>
<tr>
<td>Pain on erection</td>
<td>9/20 (45%)</td>
</tr>
<tr>
<td>IIEF (Total score = 30)</td>
<td>17.65 ± 1.52</td>
</tr>
</tbody>
</table>

The values except penile pain were expressed as mean ± SEM. Plaque density grades were obtained from self-report questionnaires. IFN α-2b = interferon alpha-2b; IIEF = International Index of Erectile Function. ns = not significant (P > 0.05).

The Impact of Intralesional Interferon α -2b Injection Therapy on Penile Hemodynamics in Men with Peyronie’s Disease: Randomized placebo controlled

“Of interest intralesional saline injections demonstrated some benefit in terms of plaque size, plaque density and pain on erection”

Single-Blind, Multicenter, Placebo Controlled, Parallel Study to Assess the Safety and Efficacy of Intrallesional Interferon -2b for Minimally Invasive Treatment for Peyronie’s Disease

- 103/117 men average age 55.1; PD for 12 months; Curve $>30^\circ$
- 53 men had placebo (saline) for 6 weeks  50 Interferon
- 5 MU every other week in 10 cc saline  for 12 weeks (6 injections/30 Mu)

| TABLE 2. Changes before and after treatment in placebo and IFN α-2b treated patients |
|---------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| **Parameter**                   | **Placebo**                   | **IFN α-2b**                  | **p Value**                   | **p Value IFN α-2b vs Placebo** |
| Mean penile curvature ± SEM (degrees) | Before 50.9 ± 2.5  After 46.4 ± 2.2  p <0.01 | Before 49.9 ± 2.4  After 38.4 ± 2.1  p <0.001 | <0.01 |
| Mean plaque size ± SEM (cm$^2$)  | Before 4.5 ± 0.55  After 3.6 ± 0.41  p <0.05 | Before 4.8 ± 0.95  After 2.2 ± 0.23  p <0.01 | <0.001 |
| Mean plaque density ± SEM (range 0–3) | Before 2.07 ± 0.12  After 1.84 ± 0.10  p <0.05 | Before 2.29 ± 0.16  After 1.52 ± 0.15  p <0.001 | <0.05 |
| Mean HEF 5+15 ± SEM (total 30)  | Before 17.98 ± 1.33  After 19.05 ± 1.32  Not significant | Before 18.32 ± 1.21  After 20.80 ± 1.19  p <0.05 | Not significant |
| % Penile pain:                      | At baseline 60.3  Resolved 28.1 | At baseline 62.0  Resolved 67.7 |

Baseline parameters were not statistically different between groups.

Hellstrom J of Urol Vol. 176, 394-398, July 2006
4.3.2.4. Interferon. Interferon α-2b has been shown to decrease fibroblast proliferation, extracellular matrix production, and collagen production from fibroblasts and improve the wound-healing process from Peyronie’s disease plaques in vitro.

Intralesional injections (5 MU units of interferon α-2b in 10 ml saline **two times** per week for 12 wk ??? significantly improved penile curvature, plaque size and density, and pain compared with placebo. Side effects include myalgias, arthralgia, sinusitis, fever, and flulike symptoms. These can be effectively treated with nonsteroidal anti-inflammatory drugs before interferon injection.
Summary on Interferon α-2b

- One single blind placebo controlled study with equivocal results
- Every study has different dosing schedule with no rationale
  - With or without saline
  - Frequency of dosing
  - Duration of dosing
- No long term safety studies
- Long term studies with cancer treatments bring in safety issues.
- Do you feel comfortable injecting a carcinogenic agent for a benign disease?
Interferon α-2b Injection – Still a Viable Option?

No!
Was it ever?
MUSTAFA, YOU ARE OUT!!!
Cost

- Intron A = $283 for 10 million Units
- Typical Treatment is 6 injections
  - CPT 54200 = 100 X 6 = $600
  - E/M 99212 = $50 X 6 = 300
- Interferon = 3 X $283 = $1698
- Total cost = $2598

- Saline 10 cc = $2.5
- Typical Treatment is 6 injections
  - CPT 54200 = 100 X 6 = $600
  - E/M 99212 = $50 X 6 = 300
  - Saline = 6 X $2.5 = $15
- Total cost = $915
Ineffective treatment of keloids with interferon alpha-2b.

- To determine the efficacy of interferon alpha-2b in keloid management, the authors prospectively evaluated the effects of interferon alpha-2b as postexcisional adjuvant therapy for keloids. Thirty-nine keloids in 34 patients were photographed, measured, and surgically excised. The wound bed was injected twice with either interferon alpha-2b (treatment group; n = 13 keloids) or triamcinolone (control group; n = 26 keloids) at surgery and 1 week later. The patients were followed up in the plastic surgery clinic.

- RESULTS:
  - The trial protocol was terminated at midtrial surveillance. Among the 13 keloids that were treated with postoperative intralesional interferon alpha-2b, seven recurred (54 percent recurrence rate). In contrast, in the 26 keloids that received triamcinolone (control group), only four recurred (15 percent recurrence rate). Recurrence in either group did not correlate with location of the keloid or race.

- CONCLUSION: Interferon does not appear to be effective in the clinical management of keloids.