LETTERS TO THE EDITOR

Low-dose oral interferon α possibly retards the progression of idiopathic pulmonary fibrosis and alleviates associated cough in some patients

Idiopathic pulmonary fibrosis (IPF) has no effective treatment and a relatively short life expectancy after diagnosis. Interferon α (IFNα) inhibits the growth of proliferating fibroblasts.1 IFNα also inhibits the production of collagen by fibroblasts independently of its effect on fibroblast replication.2 Biological activity of low-dose IFNα by oromucosal administration has been reported in several species including man,2 despite the expected rapid inactivation by digestive enzymes.3

We therefore tested the effect of oral administration of very low doses of IFNα on the progression of IPF. Twelve of 20 patients with IPF aged 50–82 years (mean 67) completed treatment for at least 12 months with IFNα administered by lozenge (150 IU) taken three times each day. IFNα was diagnosed according to the diagnostic criteria set forth by the American Thoracic Society. Three subjects had lung biopsies and all subjects had high resolution CT prior to entry into the study. All subjects had significant loss of function documented by pulmonary function tests on entry with the average baseline forced vital capacity (FVC) being 57.0% of predicted on entry with the average baseline forced oxygen saturation post-exercise being 73.4%. The other eight subjects were excluded due to non-compliance, progression of IPF, transfer to another research study, or failure to begin or complete treatment. Autopsy on the three subjects who died during treatment was consistent with deaths resulting from progression and/or complications of severe IPF.

Clinical data on the 12 subjects who completed at least 1 year of treatment are summarised in table 1. All subjects tolerated treatment well. Using the criteria from the International Consensus Statement, FVC was stable in 10 subjects (12 evaluable), and O2 saturation postexercise was stable or improved in nine subjects (11 evaluable) over a 12-month period. High resolution CTs (HRCTs) showed no evidence of progression after 1 year in seven subjects (11 evaluable) and only slight progression in the other four.

Five of the six subjects with chronic cough on entry reported an overall improvement within 2–3 weeks after starting treatment. Five of these subjects who completed the validated Leicester Cough Questionnaire had a significant improvement in their total score.5 Detailed methodology, results and other supplemental data are available online on the journal website for review.

Our study, designed as a proof of concept study, was limited by a small number of subjects and by not being placebo controlled. Treatment with low-dose, oral IFNα appeared to stop or delay progression in most subjects and markedly improved the IPF-associated cough in this uncontrolled single arm study. The potential efficacy of this low-cost, well-tolerated regimen needs to be validated in a larger double-blinded placebo-controlled trial.

Table 1 Outcomes for FVC (% predicted), O2 saturation postexercise (%) and HRCT for two successive 6 months periods and 1 year based on the International Consensus Statement criteria.*

<table>
<thead>
<tr>
<th>Subject</th>
<th>Baseline FVC</th>
<th>6 months FVC</th>
<th>12 months FVC</th>
<th>Outcomes By period†</th>
<th>Baseline O2 Sat</th>
<th>6 months O2 Sat</th>
<th>12 months O2 Sat</th>
<th>Outcomes By period†</th>
<th>Progression On HRCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49.80</td>
<td>52.50</td>
<td>52.20</td>
<td>S=S=S</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>S=S=S</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>36.70</td>
<td>38.50</td>
<td>41.80</td>
<td>S=S=S</td>
<td>85</td>
<td>78</td>
<td>82</td>
<td>W−I=S</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>73.40</td>
<td>70.30</td>
<td>72.70</td>
<td>S=S=S</td>
<td>99</td>
<td>96</td>
<td>97</td>
<td>S=S=S</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>59.00</td>
<td>59.80</td>
<td>51.00</td>
<td>S=W−S</td>
<td>61</td>
<td>63</td>
<td>60</td>
<td>I−S=S</td>
<td>Slight§</td>
</tr>
<tr>
<td>7</td>
<td>72.60</td>
<td>69.10</td>
<td>67.40</td>
<td>S=S=S</td>
<td>91</td>
<td>93</td>
<td>92</td>
<td>I−S=S</td>
<td>Slight</td>
</tr>
<tr>
<td>8</td>
<td>47.30</td>
<td>37.70</td>
<td>37.40</td>
<td>W−S=W</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>66.00</td>
<td>78.80</td>
<td>72.30</td>
<td>I−S=S</td>
<td>83</td>
<td>83</td>
<td>82</td>
<td>S=S=S</td>
<td>None</td>
</tr>
<tr>
<td>15</td>
<td>54.00</td>
<td>63.40</td>
<td>56.70</td>
<td>I=W−S</td>
<td>80</td>
<td>74</td>
<td>66</td>
<td>W=W−W</td>
<td>Slight</td>
</tr>
<tr>
<td>16</td>
<td>43.10</td>
<td>40.00</td>
<td>40.00</td>
<td>S=S=S</td>
<td>67</td>
<td>82</td>
<td>77</td>
<td>I=W−I</td>
<td>Slight</td>
</tr>
<tr>
<td>18</td>
<td>68.30</td>
<td>62.20</td>
<td>59.70</td>
<td>S=S=S</td>
<td>83</td>
<td>82</td>
<td>73</td>
<td>W=S−W</td>
<td>None</td>
</tr>
<tr>
<td>19</td>
<td>63.90</td>
<td>59.60</td>
<td>48.10</td>
<td>S=W=W</td>
<td>86</td>
<td>81</td>
<td>86</td>
<td>I=W=S</td>
<td>None</td>
</tr>
<tr>
<td>20</td>
<td>48.80</td>
<td>49.50</td>
<td>45.70</td>
<td>S=S=S</td>
<td>85</td>
<td>81</td>
<td>83</td>
<td>W=W−S</td>
<td>None</td>
</tr>
</tbody>
</table>

*Stable defined as a value less than a ±10% change for FVC and less than a ±4% point change for O2 saturation post-exercise. Values at the end of the first period were used as baseline for the second period. One-year outcomes based on ±19 and 8% for FVC and O2 saturation, respectively, comparing 12 month values with baseline.
†Outcomes are indicated by: I=improved, S=stable and W=worse for the first 6 month period, the second 6 month period and 1 year in that order.
‡Subject unable to perform 6 min walk due to physical disability and baseline HRCT lost.
§Slight progression reflects a change due to a very minimal increase in disease or a technical factor of lung image when comparing 12 month scan with baseline scan.

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Five of the six subjects with chronic cough on entry reported an overall improvement within 2–3 weeks after starting treatment. Five of these subjects who completed the validated Leicester Cough Questionnaire had a significant improvement in their total score.5 Detailed methodology, results and other supplemental data are available online on the journal website for review.

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Patient Registration Site, Texas Tech University Health Sciences Center, Lubbock, TX, USA. Patient Registration Number: 00190.

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Competing interests LOL, KMN, BWS, RR, SSB and CAJ have no conflict of interest. MJC is Vice President, Clinical & Regulatory Affairs for Amarlo Biosciences (ABI). ABI provided the interferon α lozenges tested in this study at no charge and consulted on regulatory and statistical issues.

Ethics approval This study was conducted with the approval of the Institutional Review Board of the Texas Tech University Health Sciences Center Lubbock Campus.

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Evidence for association between sarcoidosis and pulmonary embolism from 35-year record linkage study

In the last year, we have observed large pulmonary embolisms (PEs) in four of 85 patients that attended the Oxford Sarcoidosis Clinic. In addition, we note a few case reports of PEs and unprovoked thrombotic events in patients with sarcoidosis (only one referenced here), leading us to question if, compared with normal populations, patients with sarcoidosis have a higher risk of developing PE.

To explore this possibility, we performed a retrospective cohort analysis using data from the well-established Oxford Record Linkage Study. This is a database of statistical records, spanning 35 years, of all hospital admissions (including day cases) to NHS hospitals, and hospital admissions (including day cases) to NHS staffs spanning 35 years, of all hospital admissions (including day cases) to NHS hospitals, and hospital admissions (including day cases) to NHS hospitals.

The data set was collected by a team trained in epidemiology in a deidentified manner. A large numbers collected over a long period of time (1965–1998), in a deidentified population. The data set was collected by a team trained in epidemiology in a deidentified manner. A large numbers collected over a long period of time (1965–1998), in a deidentified population.

The CI for the rate ratio and its significance increased. A similar proportion was found after excluding cases of CVD and PE in the sarcoidosis group. It is known that as many as 25% of patients with sarcoidosis have cardiac involvement in which cardiac manifestations are present.

We found an increased risk of heart failure but the risk of other CVDs was not significantly increased. A similar profile was found after excluding cases of CVD and PE in the first year, and where no age restrictions were applied (see table 1).

Our observation comes from a well-established epidemiological data set comprising large numbers collected over a long period of time (1965–1998), in a deidentified population. The data set was collected by a team trained in the coding of clinical data. The population is stable, with respect to migration, forming a homogenous cohort, and has a standardised mortality ratio of 85, indicating a relatively healthy population. One limitation is the lack of scope for validation. We know little about the patients other than their International Classification of Diseases (ICD) codes (eg, sarcoidosis, PE). We have no data on diagnostic criteria, or potential confounding factors—for example, corticosteroid treatment for sarcoidosis, smoking status and other risk factors for thrombosis. In addition, these are hospitalised patients, and many sarcoidosis patients are not admitted even when the disease is active. One caveat is that this was probably not always the case, particularly early on during the cohort period when patients may have been admitted for Kveim testing.

Our data show that the incidence of heart failure was also higher than expected in the sarcoidosis group. It is known that as many as 25% of patients with sarcoidosis have cardiac involvement in which cardiac manifestations are present.

The cause for this potential increase in risk of PE is speculative, but could include use of corticosteroids, hitherto unrecognized.
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