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,[3] despite the expected rapid inactivation by digestive enzymes.[4]

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. IPF 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 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 with a range of 36.7–73.4%. The subjects were seen by a physician in the clinic on days 7, 14, 30, 60 and 90 after the start of treatment, and then at regular 3 month intervals. Serial blood work, pulmonary function tests (PFTs) and CT scans were obtained at regular intervals. The other eight subjects were excluded because of 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 O_2 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. Two subjects followed for 36 and 57 months showed stability on the PFTs and no progression on the HRCT.

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.

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Lorenz O Lutherer,[1] Kenneth M Nugent,[1] Byron W Schoettle,[1] Martin J Cummins,[2] Rishi Raj,[1] Surinder S Birring,[3] Cynthia A Jumper[1]

[1]Departments of Internal Medicine and Physiology, Texas Tech University Health Sciences Center, Lubbock, Texas, USA; [2]Amarillo Biosciences, Amarillo, Texas, USA; [3]Department of Respiratory Medicine, King's College Hospital, Denmark Hill, London, UK

Correspondence to Rishi Raj, Pulmonary, Critical Care and Sleep Medicine, Texas Tech University Health Sciences Center, 3601 4th Street, Stop 9410, Lubbock, TX 79430-9410, USA; rishi.raj@ttuhsc.edu

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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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Table 1 Outcomes for FVC (% predicted), O_2 saturation postexercise (%) and HRCT for two successive 6 month periods and 1 year based on the International Consensus Statement criteria*

Subject	Baseline FVC	6 months FVC	12 months FVC	Outcomes By period†	Baseline O_2 Sat	6 months O_2 Sat	12 months O_2 Sat	Outcomes By period†	Progression On HRCT
1	49.80	52.50	52.20	S–S–S	75	75	75	S–S–S	None
3	36.70	38.50	41.80	S–S–S	85	78	82	W–I–S	None
4	73.40	70.30	72.70	S–S–S	99	96	97	S–S–S	None
5	59.00	59.80	51.00	S–W–S	61	63	60	I–S–S	Slight§
8	72.60	69.10	67.40	S–S–S	91	93	92	I–S–S	Slight
11	47.30	37.70	37.40	W–S–W	‡				‡
12	66.00	78.80	72.30	I–S–S	83	83	82	S–S–S	None
15	54.00	63.40	56.70	I–W–S	80	74	65	W–W–W	Slight
16	43.10	40.00	40.00	S–S–S	67	82	77	I–W–I	Slight
18	68.30	62.20	59.70	S–S–S	83	82	73	S–W–W	None
19	63.90	59.60	48.10	S–W–W	86	91	86	I–W–S	None
20	49.80	49.50	45.70	S–S–S	85	81	83	W–S–S	None

*Stable defined as a value less than a ±10% change for FVC and less than a ±4% point change for O_2 saturation post-exercise. Values at the end of the first period were used as baseline for the second period. One-year outcomes based on ±changes of <19 and 8% for FVC and O_2 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.
FVC, forced vital capacity; HRCT, high resolution CT.

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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),[1] 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.[2] This is a database of statistical records, spanning 35 years, of all hospital admissions (including day cases) to National Health Service (NHS) hospitals, and all deaths, regardless of where they occurred, in defined populations within the former Oxfordshire NHS region. The database and methods used for studying disease associations have been described[2] and can also be found in the Supplementary data. The sarcoidosis cohort (n=1002) was assembled by identifying admissions during the study period where sarcoidosis was recorded as the principal diagnostic reason for admission. The reference cohort (n=526 107) comprised patients admitted for the first time for various medical and surgical conditions as the principal diagnosis[3] (see table 1). The disease and reference cohorts were matched by age, gender, year of first admission and district of residence.

Within these cohorts, we searched the database for any subsequent NHS hospital care for, or death from, (1) PE and (2) other cardiovascular disorders (CVDs) (see table 1). In subset analyses, we applied an age restriction of 65 for the sarcoidosis and reference cohort to minimise confounding co-morbidities. We also re-analysed the data excluding patients who presented with PE or other CVDs within a year of the index admission to reduce any surveillance bias (see Supplementary data).

Table 1 Occurrence of PE compared with other cardiovascular events in patients admitted to hospital with sarcoidosis, compared with a reference cohort

Outcome	Observed	Expected	RR	Lower CI	Upper CI	p Value
All ages						
AAA	2.00	2.70	0.75	0.09	2.72	0.69
CHD	44.00	43.80	1.00	0.73	1.35	0.98
Heart Failure	21.00	11.80	1.78	1.10	2.72	0.01
MI	33.00	28.60	1.15	0.79	1.62	0.41
PE	14.00	7.30	1.92	1.05	3.23	0.01
DVT	5.00	5.00	1.00	0.32	2.34	1.00
Strokes excluding SAH	21.00	18.30	1.15	0.71	1.76	0.53
SAH	2.00	2.20	0.91	0.11	3.31	0.90
Under 65 years						
AAA	2.00	2.60	0.78	0.09	2.82	0.72
CHD	36.00	37.80	0.95	0.67	1.32	0.77
Heart Failure	18.00	8.20	2.22	1.31	3.51	0.00
MI	25.00	23.90	1.04	0.68	1.54	0.83
PE	13.00	6.60	1.98	1.05	3.39	0.01
DVT	5.00	4.10	1.23	0.40	2.88	0.65
Strokes excluding SAH	17.00	12.60	1.35	0.79	2.17	0.22
SAH	2.00	2.00	1.02	0.12	3.72	0.98
All ages excluding DVT and PE diagnosed within first year of admission						
AAA	2.00	2.60	0.77	0.09	2.78	0.95
CHD	42.00	41.90	1.00	0.72	1.36	0.99
Heart Failure	20.00	11.30	1.78	1.09	2.75	0.01
MI	32.00	27.20	1.18	0.81	1.67	0.35
PE	12.00	6.50	1.87	0.96	3.27	0.03
DVT	4.00	4.50	0.89	0.24	2.29	0.82
Strokes excluding SAH	20.00	17.00	1.18	0.72	1.82	0.47
SAH	1.00	2.00	0.50	0.01	2.80	0.48

Patients in the reference cohort were drawn from a group who were admitted to hospital with squint, otitis media, haemorrhoids, deflected septum, nasal polyps, impacted tooth, ingrowing toenail, bunions, sebaceous cyst, superficial injury and appendicectomy.
AAA, abdominal aortic aneurysm, CHD, coronary heart disease; DVT, deep vein thrombosis, PE, pulmonary embolism; RR, rate ratio; SAH, subarachnoid haemorrhage.

Rate ratios were calculated, comparing rates of PE or other CVDs in the sarcoid cohort with rates in the reference cohort. The CI for the rate ratio and χ^2 statistics for its significance were calculated as previously described.[2] Further description is provided in the Supplementary data.

The risk of PE was significantly higher in sarcoidosis patients (rate ratio 2.0, 95% CIs 1.1 to 3.4, for the under 65 year olds, table 1). We also 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 (1963–1998), in a defined 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 sudden cardiac death and congestive cardiac failure are features.[4] It may be that in the cohort of patients with disease severe enough to require admission there is a greater degree of systemic 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 unrecognised