LETTERS

Association between bronchiectasis and smoking in patients with rheumatoid arthritis

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There is a well recognised association between rheumatoid arthritis (RA) and bronchiectasis. Walker observed a 10-fold increased prevalence of bronchiectasis in RA.[1] The increased incidence of pulmonary disease in his study could not be explained by the greater susceptibility to infection by patients with RA because the symptoms of bronchiectasis preceded those of arthritis in the majority of the cases. Earlier reports found the prevalence of bronchiectasis in RA to be between 1 and 10%.[1] However, with the advent of high resolution computed tomography (HRCT) of the lung, later studies reported a prevalence of 25–30%.[2 3] This is important as HRCT is a more sensitive method of detecting bronchiectasis, and it is generally accepted that a chest radiograph may be normal in patients with bronchiectasis. Secondly, later studies investigated principally lifelong non-smoking patients with RA as opposed to the earlier studies, which investigated patients with RA irrespective of their smoking history. Cigarette smoking, particularly heavy cigarette smoking, is associated with the development of seropositive RA.[4] Likewise, it has been suggested that bronchiectasis may be a trigger for the development of RA.[5] To determine if these two potential risk factors for the development of RA are distinct we used HRCT to study patients with RA to determine if there are differences in the prevalence of smoking in patients with RA and bronchiectasis.

METHODS AND RESULTS

Using HRCT, we identified 22 patients with RA with bronchiectasis (group I). We then matched these patients (group I) for age and sex with a cohort of patients with RA who had undergone HRCT of the chest as part of a larger study undertaken earlier by the department[6] (group II). All patients in group II had no HRCT evidence of bronchiectasis. Table 1 shows the results obtained.

Table 1 Characteristics of patients with RA with and without evidence of bronchiectasis

	Group I*	Group II*	p Value
Total number	21	42	N/A
Sex (F/M)	18/3	36/6	N/A
Age (years), mean (SD)	59.4 (9.9)	60.1 (9.8)	N/A
Duration of RA (years), mean (SD)	16.8 (11.0)	14.3 (8.5)	0.5
HAQ score (range 0–3), mean (SD)	1.8 (0.8)	1.6 (0.8)	0.5
Rheumatoid factor positive, No (%)	16 (76)	33 (79)	1.0
ANA positive, No (%)	2 (10)	11 (26)	0.2
CRP (mg/l), mean (SD)	25.1 (17.9)	21.2 (21.2)	0.4
Haemoglobin (g/l), mean (SD)	132 (17)	130 (12)	0.8
Receiving methotrexate, No (%)	11 (52)	18 (43)	0.6
Smokers, No (%)	4 (19)	18 (43)	0.09
Ex-smokers, No (%)	5 (24)	13 (31)	0.8
Non-smokers, No (%)	12 (57)	11 (26)	0.026*
Smoking (pack-years), mean (SD)	9.2 (15.5)	21.4 (18.0)	0.007*

*Group 1, RA+bronchiectasis; group II, RA−bronchiectasis.

This study disclosed a significant difference in smoking between the two groups, with a greater tendency for those in the group with bronchiectasis to be non-smokers. There was also a significant difference in smoking when expressed as pack-years between the two groups. This is in keeping with previous studies showing a high incidence of bronchiectasis on HRCT in non-smoking patients with RA.[2] Patients with bronchiectasis in the population generally tend to be non-smokers. A study investigating the predisposing factors for the development of bronchiectasis in 69 patients found that 50 of them were non-smokers.[6] This is presumably because the symptoms of bronchiectasis,[7] such as production of copious amounts of sputum daily, frequent severe chest infections, and wheezing, are not conducive to a desire to smoke. A survey of publications between 1985 and 2001 did show an irrefutable link between smoking and RA.[8] Possibly, patients with RA and bronchiectasis stop smoking because of deteriorating lung function. However, significantly more of the patients in the study group were non-smokers than ex-smokers.

DISCUSSION

There are a number of potential mechanisms by which bronchiectasis might trigger RA. The presence of bronchiectasis is consistent with a persistently active inflammatory process, and increases in CD 4+ T lymphocytes, macrophages, and neutrophils, and interleukin 8 positive cells have been found in the airways of patients with bronchiectasis.[9] The priming of these inflammatory cells within the bronchiectatic lung might result in an increase of circulating proinflammatory cells and predispose to RA. Based on the results of this study and others, it is tempting to speculate that bronchiectasis is a strong risk factor for the development of RA, particularly in those who have never smoked.

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Successful treatment with fenofibrate, a peroxisome proliferator activated receptor α ligand, for a patient with rheumatoid arthritis

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Advances in the treatment of rheumatoid arthritis (RA), especially the introduction of biological agents such as tumour necrosis factor α (TNFα) receptor antagonists, neutralising antibodies against TNFα, and interleukin (IL)1 receptor antagonists, have dramatically delayed the progression of this disease.[1–3] Although these agents are clearly beneficial to patients with RA, the prices of these treatments are currently three times the cost of the most expensive conventional disease modifying antirheumatic drug (DMARD).[4] Therefore, if a new combination therapy could be developed using conventional DMARDs and other conventional drugs, and if this treatment were as effective as, but less costly than, the biological agents, this would be ideal. We describe a patient with RA for whom methotrexate treatment was no longer effective, and who received anti-hyperlipidaemia treatment with fenofibrate, a peroxisome proliferator activated receptor (PPAR) α ligand. This treatment eventually resulted in an improvement in her symptoms. This case suggests that fenofibrate together with methotrexate may be a feasible combination treatment for RA.

CASE REPORT

A 33 year old woman with RA was evaluated in October 2000 for a worsening polyarthritis that had been resistant to treatment for many years. She was noted to have mild hyperlipidaemia. RA had been diagnosed when she was 19 years old. She had had six months of swelling, pain, and stiffness of the second and third metacarpophalangeal joints bilaterally. She was given metalcaptase (400 mg) for 1 year with no improvement of symptoms, and then switched to bucillamin (200 mg/day) for 3 years, again with no improvement. Finally, she was given methotrexate (5–8 mg/week) in addition to bucillamin (200 mg/day) and prednisolone (10 mg/day) beginning in 1994, and this resulted in some benefit. During the course of her treatment with these drugs, her baseline C reactive protein (CRP) level was 30–80 mg/l, and her mean pain visual analogue scale (VAS) score was 78 mm. The mean Health Assessment Questionnaire (HAQ) score was 1.87 and the mean painful joint count was 14.5.

Treatment with fenofibrate (300 mg/day) was started, in addition to the previous treatment with methotrexate (8 mg/week: the maximum dose in Japan), bucillamin (200 mg/day), and prednisolone (10 mg/day), in July 2001. After starting the combination therapy, her symptoms apparently improved and her VAS score improved to around 40 mm. Changes in other measures used to evaluate the disease activity of RA included the patient's global assessment (from about 50 mm to about 30 mm), the physician's global assessment (from about 70 mm to about 20 mm), the HAQ (from about 2 to about 1.5), painful joint count (from about 15 to about 5), and CRP (from about 45 mg/l to about 10 mg/l). Figure 1 shows the way in which each of these improved.

From July 2001, treatment with fenofibrate (300 mg/day) was started, in addition to the previous treatment with methotrexate (8 mg/week), bucillamin (200 mg/day), and prednisolone (10 mg/day).

The patient has now been followed up for 3 years, and over this period corticosteroid was gradually tapered to 8 mg/day and bucillamin (200 mg/day) was discontinued. Fenofibrate (300 mg/day) together with methotrexate (8 mg/week) were continued as maintenance treatment. Thus far, there have been no adverse reactions to this combination therapy.

DISCUSSION

We describe here a case of RA that had been resistant to conventional treatment for many years. The patient eventually received anti-hyperlipidaemia treatment with fenofibrate, a PPAR α ligand, and this was found to be beneficial for the treatment of her RA.

RA is characterised by massive synovial proliferation and subintimal infiltration of inflammatory cells, followed by the destruction of cartilage and bone. Inflammatory mediators such as IL6, IL1, and TNFα play important roles in the pathogenesis of RA. The NF-κB family of transcriptional activators regulates the expression of a variety of cytokines involved in osteoclast differentiation, including IL1, TNFα, and IL6.[5] The anti-hyperlipidaemia drugs, 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (statins), have been shown to inhibit the development of collagen induced arthritis by suppression of the Th1 immune response.[6] This observation is compatible with other in vitro studies in which the major histocompatibility complex class II transactivator was suppressed and T cell costimulation was also suppressed through direct allosteric inhibition via an integrin L-site.[7 8] On the other hand, another anti-hyperlipidaemia drug, PPAR α ligand, has been reported to inhibit IL1 induced production of IL6 and prostaglandin, and they inhibit expression of

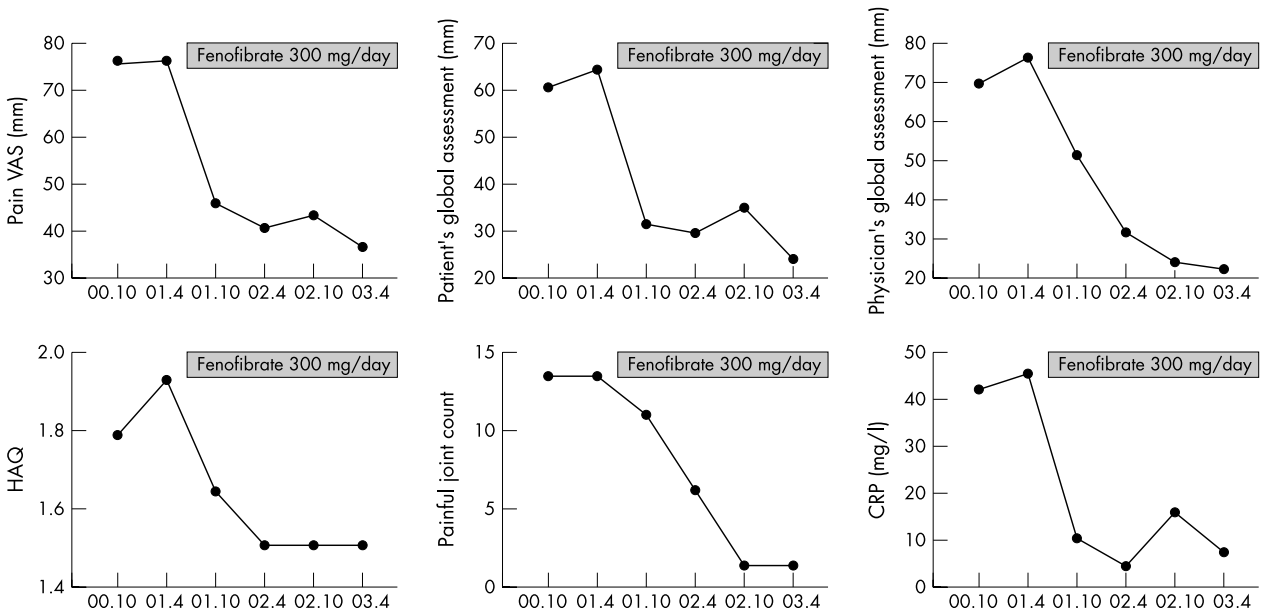

Figure 1 Clinical parameters before and after treatment with fenofibrate.

cyclo-oxygenase-2 by negatively interfering with NF-κB transcriptional activity.[9] We believe that fenofibrate together with methotrexate may be a feasible combination therapy, and may be a new strategy for the treatment of RA.

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