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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

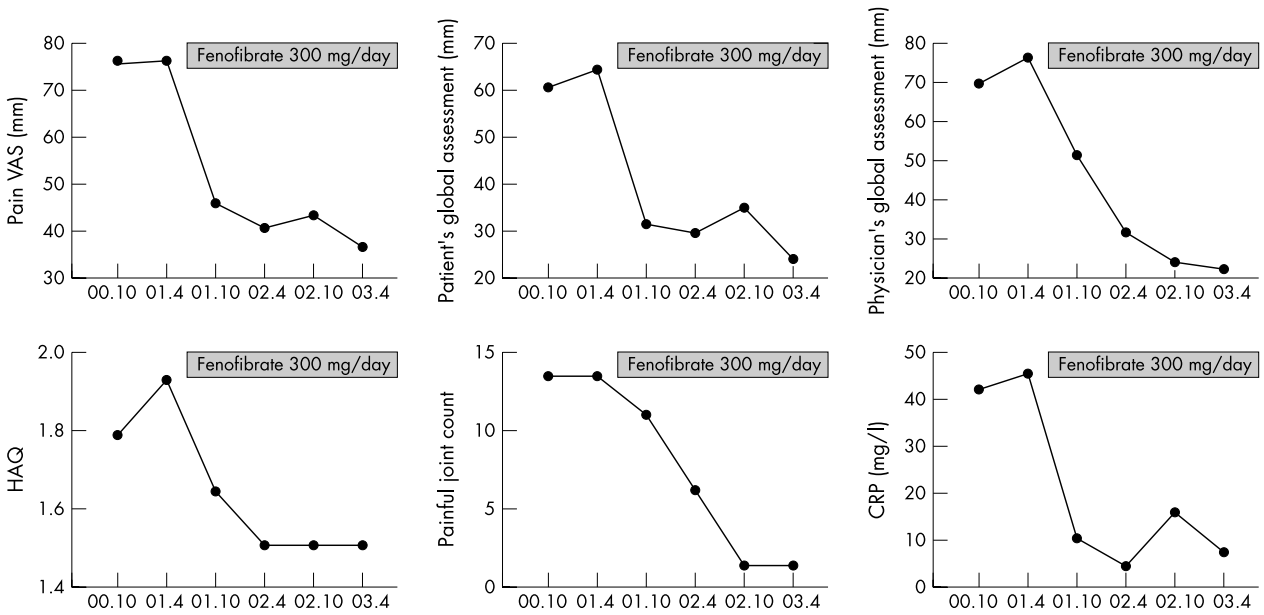

Figure 1 Clinical parameters before and after treatment with fenofibrate.

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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