

## CONCISE REPORT

# Rheumatological complications associated with the use of indinavir and other protease inhibitors

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Several cases are reported of rheumatological pathology (temporomandibular dysfunction, frozen shoulder, Dupuytren's disease, and tendinitis) most probably related to the intake of indinavir in HIV positive patients. A survey using an anonymous questionnaire of 878 people with HIV infection treated with antiretroviral drugs suggests that other protease inhibitors may also cause arthralgia.

The use of protease inhibitors is an important part of the management of HIV infection. However, they have been associated with long term side effects such as lipodystrophy. Other side effects, such as nephrolithiasis,<sup>1</sup> hair loss, and paronychia,<sup>2</sup> seem to be more specifically related to indinavir. Recently, ten cases of frozen shoulder associated with indinavir have been reported.<sup>3–7</sup>

In this report we describe four cases of HIV infected patients who developed rheumatological complications during indinavir treatment. Moreover, in a survey of patients with HIV infection treated with an antiretroviral, we also found an association between arthralgia and the use of other protease inhibitors.

### CASE 1

A 57 year old woman was found to be HIV seropositive in February 1997 and started antiretroviral treatment (indinavir 800 mg three times a day, stavudine 40 mg twice a day, and lamivudine 150 mg twice a day) in July 1997. In October 1997, she developed lipodystrophy, hair loss, and intermittent arthralgias.

In November 1997, she began to complain of difficulty in opening her mouth, with stiffness and decreased translation motion. A computed tomography scan of the temporomandibular region showed small erosions at the top of the mandibular condyle. A possible association with indinavir was ruled out by the consultant stomatologist who diagnosed a temporomandibular dysfunction attributable to a problem with dentures. He recommended anti-inflammatory drugs and a dental splint.

Given the lack of results, the patient consulted another stomatologist who advised changing the dentures. Eighteen months after the introduction of combination treatment, she was still suffering from temporomandibular dysfunction despite the local treatment. At that point, we decided to replace indinavir with nelfinavir.

Within a few days, the patient reported a substantial improvement in chewing function and reduction in pain. After one week, she was able to open and move her mouth normally but a small degree of pain persisted. Because of incapacitating diarrhoea, the nelfinavir was stopped. Since November 1999, the patient has been receiving a protease inhibitor sparing regimen with nevirapine, a non-nucleoside analogue, stavudine, and lamivudine. The pain and reduction in jaw mobility have not resumed.

### CASE 2

A 47 year old man was found to be HIV seropositive in 1987. He began a triple therapy regimen in August 1996 (indinavir 800 mg three times a day, lamivudine 150 mg twice a day, and stavudine 150 mg twice a day) because of a very low CD4 lymphocyte count ( $4/\mu\text{l}$ ) and a high viral load (180 000 copies/ml). In February 1997, he developed a frozen shoulder on the right side. He improved partially with physiotherapy and intra-articular injections. In November 1996, he presented with the same problem on the other side. A consultant rheumatologist could not find any cause and advised continuation with the conservative treatment.

In February 2000, indinavir was changed to nevirapine because of microhaematuria and kidney pain. His CD4 lymphocyte count was then  $616/\mu\text{l}$  and his viral load was undetectable ( $<50$  copies/ml). He is now pain free and his shoulder mobility is normal.

### CASE 3

A 46 year old man was diagnosed with HIV in 1986 and treated with zidovudine and zalcitabine. In August 1996, his CD4 lymphocyte count was  $24/\mu\text{l}$  and his viral load was above the detection limit of the test ( $>750$  000 copies/ml). He was then put on tritherapy (indinavir 800 mg three times a day, lamivudine 150 mg twice a day, and stavudine 40 mg twice a day).

In January 1997, he was diagnosed with a frozen shoulder. Later on that year he developed Dupuytren's disease in both hands and lipodystrophy syndrome. He was treated with physiotherapy and intra-articular injections, and the shoulder complaints decreased.

He was switched from indinavir to nevirapine in January 2000 as he had developed grade II hydronephros as the result of nephrolithiasis. At that time, he had a CD4 lymphocyte count of  $622/\mu\text{l}$  and a viral load below 50 copies/ml. Since then he has not complained of shoulder pain or movement reduction. The Dupuytren's disease has also improved considerably since the switch to the non-nucleoside analogue.

### CASE 4

A 40 year old man was found to be HIV positive in 1997 with a low CD4 lymphocyte count ( $54/\mu\text{l}$ ) and a high viral load (527774 copies/ml). Tritherapy was started (indinavir 800 mg twice a day, lamivudine 150 mg twice a day, and stavudine 40 mg twice a day) in July 1997. In November 1999, the patient asked to be put on a twice a day therapy. He then started a combination of two protease inhibitors, indinavir and ritonavir in association with the same two nucleoside analogues. However, by mistake he took double doses of indinavir (1600 mg twice a day) and ritonavir (200 mg twice a day). His CD4 lymphocyte count was  $480/\mu\text{l}$  and the viral load was below 50 copies/ml. After three days, he developed several episodes of renal colic, haematuria, and acute pain in the right wrist. The latter was diagnosed as De Quervain tendinitis. A blood test showed normal urea, creatinine, transaminases, and uric acid.

**Table 1** Survey of 878 patients with HIV infection in Europe: complaints of arthralgia since the start of current antiretroviral treatment

Treatment regimen	Arthralgia		Total
	n	%	
Protease inhibitors	239	35.5*	674
Indinavir	104	40.6*	256
Nelfinavir	72	36.2*	199
Ritonavir alone	9	22.0	41
Saquinavir alone	12	21.4	56
Ritonavir + saquinavir	31	41.9*	74
Other combinations	11	22.9	48
Non-nucleoside reverse transcriptase inhibitors	31	26.5	117
Only nucleoside transcriptase inhibitors	22	25.3	87

\*Significantly higher ( $p < 0.05$ ) than among patients receiving non-protease inhibitor treatment.

The symptoms subsided after interruption of the antiretroviral drugs for five days. Once the patient was better, his previous treatment was started again; the side effects did not reoccur.

### EUROPEAN SURVEY

Between December 1998 and December 1999, we performed a multicentre survey among adult outpatients with HIV infection in 10 European countries using an anonymous questionnaire. The survey addressed different aspects of HIV care. Participants were asked about symptoms and signs that had appeared since the start of their current antiretroviral treatment. Arthralgia was defined as "pain in the joints". There were no specific questions about Dupuytren disease or other rheumatological diseases. The complete methodology of this survey has been described previously.<sup>8</sup>

Most of the study participants were men (80%). The mean age of the study population was 39 years. More than half (55%) of the respondents reported HIV transmission through male homosexual contact, 22% reported having been infected by heterosexual contacts, and 16% by intravenous drug use. The mean time since HIV diagnosis was eight years. At the time of the study, 55% of the patients were asymptomatic, 30% were symptomatic without AIDS, and 15% had AIDS. Some 22% of the participants had a CD4 lymphocyte count of less than 200/mm<sup>3</sup>, and 43% had an undetectable viral load (detection limit 500 copies/ml). In total, 257 respondents (22.1%) were not receiving antiretroviral treatment at the time of the study. Of 878 patients using antiretroviral drugs, 674 (77%) had been treated with protease inhibitors for an average of 15 months.

Arthralgia was more often reported by patients on a treatment regimen containing a protease inhibitor than by patients on a non-protease inhibitor containing treatment (239 (35.5%) *v* 53 (26%);  $p = 0.01$ ). Patients treated with indinavir, nelfinavir, and the ritonavir-saquinavir combination reported arthralgia significantly more often than those receiving non-protease inhibitor treatment (including a non-nucleoside reverse transcriptase inhibitor) (table 1). Significant variables in univariate analysis—that is, age, disease stage, disease duration, and current antiretroviral treatment—were included in a multivariate analysis corrected for previous antiretroviral therapy. Using this model, arthralgia remained highly associated with the current use of indinavir ( $p = 0.0006$ ) and the ritonavir-saquinavir combination ( $p = 0.02$ ).

### DISCUSSION

This is the first report of a temporomandibular dysfunction associated with protease inhibitor use. The rheumatological complaints only disappeared completely when the protease inhibitors were replaced with nevirapine, a non-nucleoside analogue. The temporal association and the fact that the patients were experiencing other side effects related to the use

of protease inhibitors are strong arguments for citing the protease inhibitors as a potential cause of these disorders.

Mild rheumatological symptoms, including aspecific arthralgia and non-erosive oligoarthritis, were commonly reported among HIV infected children and adults before the introduction of highly active antiretroviral therapy.<sup>9-11</sup> Dupuytren's disease has also been associated with HIV infection.<sup>12</sup> Tendinitis is occasionally associated with the intake of various medications such as fluoroquinolones<sup>13</sup> or calcium channel blockers.<sup>14</sup> The pathogenesis of frozen shoulder and Dupuytren's disease is unclear. An active fibroblastic proliferation caused by transforming growth factor  $\beta$  has been found in both conditions,<sup>15</sup> but the cause of these disorders often remains idiopathic. Indinavir is known to crystallise in the urinary tract causing urolithiasis, and indinavir crystals have also been found in joint fluid of patients with frozen shoulder.<sup>5, 16</sup> The same phenomenon of intratissue crystallisation as seen in gout could trigger the inflammatory pathways and lead to the osteoarticular manifestations described above.

The survey of people with HIV infection in Europe also suggests that protease inhibitors such as indinavir and maybe others may cause arthralgia. To confirm this hypothesis, patients in randomised HIV clinical trials should be systematically examined for rheumatological disorders.

If a person with HIV infection treated with a protease inhibitor develops a rheumatological disorder, it is important that doctors take into consideration that these complaints may be drug related. In such a patient, a temporary interruption of the protease inhibitor and switch to another class of antiretroviral drug should be considered to prove causality. The case reports described in this paper show that, to treat an HIV infected person who has a rheumatological disorder, a good collaboration between the rheumatologist and the HIV expert is essential.

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