Bone involvement in psoriatic arthritis.

Bernard Cortet, Marie-Hélène Trouvé and René-Marc Flipo

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Methotrexate as a Possible Trigger of Macrophage Activation Syndrome in Systemic Juvenile Idiopathic Arthritis

To the Editor:

We read with interest the article by Ravelli, et al., describing a patient with systemic juvenile idiopathic arthritis (SJIA) who developed a clinical picture and laboratory abnormalities compatible with the diagnosis of macrophage activation syndrome (MAS).

The disturbing statement suggesting the possibility that methotrexate (MTX) could be responsible for this severe complication motivated us to search through Medline for other reported cases and to consider other possible triggers of MAS in this patient. With this objective we believe it important to emphasize some aspects of this case report.

First, the marked increase in the serum ferritin level deserves further consideration. Hyperferritinaemia is a very good marker of activity in adult onset Still’s disease, and to a lesser extent in SJIA (juvenile onset Still’s disease)². Increased serum levels of ferritin may be the result of several factors including increased synthesis of ferritin by proliferated and erythropoietic monocytes-macrophages and ferritin released from the various tissues damaged by chemical factors from activated monocytes-macrophages. Taking these factors into consideration we find it reasonable to assume that the activity of the disease per se could have been the trigger of MAS in this patient.

On the other hand, low dose MTX has become widely used for both JIA and rheumatoid arthritis, and it is now often the first agent selected in children with established JIA. The toxicity profile of this agent is well known and has been the subject of numerous reports. Extensive research in Medline entries for the past 15 years failed to reveal reports with similar experience to Ravelli, et al.’s report, with the exception of a 14-year-old boy, described by the same group, who developed MAS 2 weeks after an 11-month course of oral MTX. The causal association of MTX and MAS in this other patient is also uncertain.

In view of the above concerns, we are reluctant to accept that MTX may induce MAS. Low dose MTX is an invaluable therapeutic modality for the management of JIA and several other rheumatic disorders, and while it is important to encourage the continuous surveillance and reporting of adverse side effects, it is also important, and prudent, to avoid generating undue alarm regarding uncertain and not well proven effects.

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REFERENCES


Drs. Ravelli and Martini reply

To the Editor:

Dr. Eraso, et al. assume that in our patient the activity of the disease itself, and not methotrexate (MTX), could have been the trigger of macrophage activation syndrome (MAS). They base their hypothesis on the fact that serum ferritin levels were high and that hyperferritinemia has been shown to be a marker of disease activity in systemic juvenile idiopathic arthritis (SJIA). Although we thank Dr. Eraso and colleagues for their interest in our observation, we cannot share their opinion. Indeed, although it is true that hyperferritinemia represents a marker of disease activity in SJIA, it is also true that it represents one of the laboratory hallmarks of MAS. Indeed, during MAS, serum ferritin levels reach values that are often much higher than those observed during active SJIA. In our patient, serum ferritin concentration, which was high (207 ng/ml) when her disease was very active (with fever, rash, polyarthritis, erythrocyte sedimentation rate 89 mm/h, and C-reactive protein at 9.9 mg/l) increased to 10,143 ng/ml at the time of the development of MAS. Recently, by reviewing the literature as well as our personal experience on JIA associated MAS, we found that a serum ferritin level ≥ 10,000 ng/ml has one of the highest sensitivity and specificity among the clinical and laboratory variables that could be regarded as potential diagnostic criteria for this complication (unpublished observation).

Therefore, in our opinion, the high serum ferritin levels cannot be taken as evidence to support the hypothesis that disease activity was the trigger of MAS in our patient. This, of course, does not mean that we can exclude such hypothesis. The triggers of MAS are unknown and may be related to disease activity, exogenous factors, or a combination of both. In previous observation in SJIA, the causal involvement of exogenous factors, such as...
To continue please scroll to next page
infections of drugs, in triggering MAS has always been based on a close temporal relation in the absence of other potentially eliciting factors.

As stated in our paper, we could not find any evidence that nonsteroidal antiinflammatory drug therapy, viral infection, or disease flare could have been responsible for the development of this complication. On the contrary, the short time interval between MTX dosing and the occurrence of clinical signs of MAS and the characteristics of clinical symptoms, which were consistent with hypersensitivity or idiiosyncratic reaction, suggested that MTX could have been the trigger of MAS in our patient. As Dr. Eraso, et al point out, the causal association between MTX and MAS was less clear in the patient previously reported by our group\(^4\). However, in that patient the time course of the clinical events also suggested a link between MTX toxic effects and the development of MAS, although the time interval was greater than in the present one.

We understand the concerns of Dr. Eraso, et al, who express their reluctance to accept the notion that MTX may induce MAS. We were also prudent in claiming this association by indicating MTX in the title of the paper as “possible” trigger of MAS in SJJIA. Nevertheless, other exceedingly rare complications of MTX therapy, such as acute pneumonitis and Hodgkin’s lymphoma, have been reported in children with JIA\(^6\). Because children with SJJIA are known to be extremely vulnerable to toxic events and distinctively susceptible to the development of MAS and several drugs have been incriminated as possible triggers of this complication, it is perhaps not unexpected that an adverse reaction to MTX may under certain circumstances elicit a MAS. With our report, we do not wish to generate undue alarm regarding MTX side effects, but simply convey to the pediatric rheumatology community a clinical observation that led us to suspect that MTX may act as an inciting factor of MAS in children with SJJIA.

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REFERENCES


Macrophage Activation Syndrome Is Hemophagocytic Lymphohistiocytosis — Need for the Right Terminology

To the Editor:

We read with great interest the paper by Ravelli, et al\(^5\). While we agree with the authors that methotrexate could possibly trigger macrophage activation syndrome (MAS) in systemic onset juvenile idiopathic arthritis (JIA), we would like to see the term MAS replaced by hemophagocytic lymphohistiocytosis (HLH). Historically the term MAS has been used to describe this potentially life threatening complication associated with systemic JIA. In 1987 the Writing Group of the Histiocyte Society recommended a division of the histiocytic disorders into 3 classes to include primary and secondary causes of hemophagocytosis like that seen in systemic JIA\(^6\).

We feel it is important for the pediatric rheumatology community to use the same terminology as pediatric hematologists to avoid confusion. Also, literature searches will enable more articles, particularly ones written by hematologists, to be picked up. It may also encourage pediatric rheumatologists to consider treatment options successful in treatment of other HLH syndromes for refractory cases. Several causative genes have recently been described with the primary form of HLH\(^6\). Hemophagocytosis is seen as a secondary phenomenon in a number of autoimmune conditions, and looking at all of them in conjunction with systemic JIA may lead to better understanding of this potentially life threatening complication.

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REFERENCES


Drs. Ravelli and Martini reply

To the Editor:

We thank Dr. Ramanan and colleagues for their interest in our report. The term macrophage activation syndrome (MAS) is commonly used to identify the hemophagocytic syndrome that may develop in children with chronic rheumatic diseases, particularly systemic juvenile idiopathic arthritis. Because MAS belongs to the group of hemophagocytic syndromes that are associated with an underlying systemic disease, such as immunodeficiency, hematological neoplasia, or autoimmune disorders, we believe that the proposal of Dr. Ramanan and colleagues to rename MAS according to the classification of histiocytosis syndromes in children warrants consideration. The choice of the more suitable term to label this complication of chronic rheumatic diseases should be important for future discussion.

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Prevalence of Spondyloarthropathy in Japan

To the Editor:

The recent report of Hakuda, et al\(^6\) concluded that the annual incidence and the prevalence of spondyloarthropathy (SpA) in Japanese were less than 1/10 and 1/200, respectively, of those among Caucasians. Since any prevai-
Table 1. Incidence rate and prevalence of AS and SpA as found in hospital-based studies and as found by intensive search in blood donor or population studies.

<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence rate per 100,000 person-years</th>
<th>Prevalence found in hospital-based studies</th>
<th>Prevalence including routinely undetected cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AS</td>
<td>SpA</td>
<td>AS</td>
</tr>
<tr>
<td>Japan1</td>
<td>≤ 0.33*</td>
<td>≤ 0.48*</td>
<td>≤ 0.0065%*</td>
</tr>
<tr>
<td>Berlin, Germany2</td>
<td></td>
<td></td>
<td>0.9%**</td>
</tr>
<tr>
<td>Netherlands3</td>
<td></td>
<td></td>
<td>0.1%***</td>
</tr>
<tr>
<td>Minnesota4</td>
<td>7.3</td>
<td></td>
<td>0.13%</td>
</tr>
<tr>
<td>Finland5</td>
<td>6.9</td>
<td></td>
<td>0.15%**</td>
</tr>
<tr>
<td>Brittany, France6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany (this letter)</td>
<td></td>
<td></td>
<td>0.12%***</td>
</tr>
</tbody>
</table>

* Under the assumption that at least 10% of all SpA patients are registered in the hospitals considered.
** Prevalence among the adult part of the population.
*** Under the assumption that the proportion of 15% members of the patient organization is representative.

ience divided by the corresponding annual incidence roughly indicates out of how many years after diagnosis the patients were included into the prevalence study (average observation period, maximally from diagnosis to death), their conclusions would imply a 20-fold longer observation period in Caucasian than in Japanese patients with SpA. This is highly unlikely.

In the Japanese study1, a SpA prevalence of 9.5/100,000 and an incidence rate of 0.48 per 100,000 person-years were reported, resulting in a ratio of 19.8 years. As may be seen in Table 1, this is in accord with the prevalence-to-incidence ratios of 18-22 years reported for ankylosing spondylitis (AS) in other studies. Thus the discrepancy must be connected with the connection made between Japanese and Caucasians. The prevalence of SpA in Japanese was estimated on the basis of hospital derived data, whereas the prevalence in Caucasians used for comparison was taken from a blood donor study2. As shown by Gran2 and by Boyer3, hospital based studies usually reveal only the more severe and typical cases normally diagnosed in clinical routine, whereas in blood donor studies or population surveys a greater insight into the full disease spectrum is gained by including more cases that normally remain undiagnosed in clinical routine.

Data on the total prevalence of SpA in Caucasians are rather limited. On the basis of the blood donor study4 and a population based survey5, values between 0.47% and 1.9% have been reported. A way to derive the prevalence of AS and SpA from limited hospital data has been reported6. According to the national database (25,852 patients with inflammatory rheumatic diseases) of the German collaborative arthritis centers7, 15% of the AS patients registered in this database are members of the AS society in Germany (Deutsche Vereinigung Morbus Bechterew, DVMB). In the same year, the DVMB membership register counted 14,239 patient members. Under the assumption that the degree of organization in the self-help society of the patients registered in the national database is representative for all diagnosed AS patients in Germany, a total of about 95,000 diagnosed AS patients = 0.12% of the general population (82 million for Germany8) can be calculated. As already mentioned, this result strongly depends on the representativeness of the 15% proportion of DVMB members in the national database. Possibly, relatively more DVMB members than patients who do not make use of the information distributed by the patient organization consult the highly specialized centers contributing to the national database.

Thus, the real prevalence of diagnosed AS may be essentially higher. Nevertheless, this way to estimate the prevalence of a disease seems interesting enough to be reported and, moreover, the rate of membership in a patient organization can easily be assessed in future trials.

The ratio between the prevalence of AS and SpA has been reported to be about 1:2, and the same ratio was found in the national database9,10. In Japanese1 this ratio was found to be 1:1.5. One reason for the difference may be the low number of undifferentiated SpA detected11. These proportions highlight that AS is the most frequent SpA subtype. If these ratios are taken into account, the ratio of 1:30 between the prevalence of AS in Japanese and Caucasians reported12 and the ratio of 1/200 for SpA contradict each other.

Using the ratio of 1:2 between the prevalence of AS and SpA as indicated above, the prevalence of diagnosed SpA patients in Germany can be estimated to be at least 190,000 = 0.23% of the general population (Table 1).

It has to be stressed once more that the prevalence of diagnosed AS or SpA reported in hospital based studies probably does not reflect the true prevalence. As shown13, AS in women has been underdiagnosed in former decades, and this underdiagnosis governs the percentage of women among diagnosed AS patients even today. Further, a comparison of the age distribution of the DVMB membership with that expected from the age distribution of the German population14 and from the distribution of the age at diagnosis of AS shows that male AS patients older than 65 years are also underrepresented in the patient organization15. This may indicate that AS was underdiagnosed in former decades in men as well. Further, the lack of appropriate therapies may have prevented a considerable number of patients consulting the rheumatological centers.

In addition, it has to be stressed that the lifetime incidence of the disease is always higher than the prevalence based on the whole population. A prevalence of 0.12% and 0.23% for AS and SpA, respectively, means that at least 0.21% and 0.41% of the population will be diagnosed with AS or SpA, respectively, during their lifetime16.

All these points lead to an underestimation of the prevalence of AS and SpA, which is probably essentially higher than the values indicated in Table 1. Accordingly, higher prevalence values for AS and SpA in Caucasians than those found in hospital based studies have been reported in population based studies17.

Nevertheless, by comparing the results shown in Table 1, it seems that the annual incidence and the prevalence of AS and SpA in Japanese are less than about 1/20 of those among Caucasians. The reportedly lower prevalences of HLA-B2718 and of psoriasis19 in Japanese certainly contribute to this result.

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REFERENCES
Drs. Hukuda and Shichikawa reply

To the Editor:

We greatly appreciate the kind and excellent comments from Dr. Feldtkeller and Dr. Braun on our study of SpA in Japan. Their arguments concern 2 points: (1) improper selection of a Western paper for international comparison of prevalence of SpA and (2) surveys based on hospital derived data.

The problem we encountered in comparing our data with Caucasian data was the limited number of epidemiological studies available for our purpose even in the Western literature. The survey by Dr. Braun and colleagues in blood donors\(^*\) was the only study we could identify at the time on Medline Express. Unfortunately we did not notice the unlikely discrepancy between incidence and prevalence from the viewpoint of observation length in our conclusions. After learning that the prevalence of SpA is 0.21% in the USA (Lawrence\(^*\)), 0.23–0.4% in Germany (Feldtkeller), and 0.47% in France\(^*\), we agree that the figure of 1.9% (Braun) is too high and specific, in that 19 out of 20 patients with SpA from among blood donors are HLA-B27 positive. Since the figure of 0.23% also came from Germany, it is more proper to take this as the comparison counterpart as Dr. Feldtkeller suggests, and we completely agree with him.

We agree with Dr. Feldtkeller and Dr. Braun in their view that the discrepancy of prevalence ratio of AS and SpA between Germany (2.0) and Japan (1.5) is due to the scarcity of undifferentiated SpA (USpA) in the latter. We are surprised to see that their USpA cases are all HLA-B27 positive. On the other hand, the AS/SpA ratio revealed by a national survey in the US was 1.6 and similar to ours, although they excluded USpA\(^*\). Therefore the figure of 0.0095% that we proposed as the prevalence of SpA based on several assumptions might be regarded as close to prevalence, based on population study, despite our hospital based survey method. This is what we think at present, but it should be ascertained by a population study in the future since prevalence may be influenced by the change of diagnostic criteria as well as the process of time.

Shichikawa, a coauthor of our study, conducted a population study between 1961 and 1992 (unpublished in Western literature) on rheumatic diseases in several cities, towns, and villages in the Kinki district, in central Japan. His survey revealed only one case of AS with peripheral involvement among 17,931 adults (0.0050%). This is quite close to the prevalence of AS estimated in the present survey. Another population study by Shichikawa performed in a countryside community revealed no radiographic sacroiliitis among 3000 male inhabitants above the age of 30 years. These data also underscore the rarity of this disease in Japan and are thought to support our assumption in the present study.

However, more precise international comparison requires more information. That RA and SpA have almost the same frequency in France indicates the prevalence of this disease is expected to rise in Europe as well as in Japan when its diagnosis becomes easier and awareness of AJ among medical professionals is further promoted. It is of great interest for us to determine the prevalence of SpA in our country, where incidence of HLA-B27 is extremely low.

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REFERENCES


Bone Involvement in Psoriatic Arthritis

To the Editor:

We read with interest the article by Frediani, et al\(^*\) reporting a high occurrence of low bone mass in patients with psoriatic arthritis (PsA). We also performed a cross sectional study in which we assessed whether patients with PsA had both bone mass and bone metabolism abnormalities. Our study group included 24 patients consecutively enrolled over a 9 month period with peripheral PsA fulfilling the criteria of Wright and Moll\(^*\). There were 12 men and 12 women (6 of them were menopausal). The following measurements of activity or severity of PsA were determined: morning stiffness duration, number of painful and swollen joints, Ritchie Articular Index\(^*\), Health Assessment Questionnaire score\(^*\), short form of the Arthritis Impact Measurement Scales 2 (AIMS-2SF-2)\(^*\), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level. Calcium intakes, alcohol consumption, and the level of physical activity were also recorded. Bone mineral density (BMD) was measured by dual-energy x-ray absorptiometry on a Hologic QDR-2000\(^*\) (Hologic, Waltham, MA, USA) at the lumbar spine and the nondominant femoral neck. Quantitative ultrasound (US) measurements were performed on the nondominant heel with an Achilles\(^*\) instrument (Lunar, Madison, WI, USA). Two variables were measured: broadband ultrasound attenuation

Correspondence

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Table 1. BMD and bone ultrasound measurements for patients with PsA and controls.

<table>
<thead>
<tr>
<th></th>
<th>PsA, n = 24</th>
<th>Controls, n = 48</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>50.2 ± 9.1</td>
<td>50.8 ± 8.8</td>
<td>0.8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.6 ± 4.9</td>
<td>24.8 ± 4.4</td>
<td>0.5</td>
</tr>
<tr>
<td>BMD lumbar spine, g/cm²</td>
<td>0.98 ± 0.15</td>
<td>1.04 ± 0.14</td>
<td>0.08</td>
</tr>
<tr>
<td>Lumbar spine T score</td>
<td>−0.7 ± 1.4</td>
<td>+0.3 ± 1.3</td>
<td>0.006</td>
</tr>
<tr>
<td>BMD femoral neck, g/cm²</td>
<td>0.78 ± 0.13</td>
<td>0.84 ± 0.12</td>
<td>0.06</td>
</tr>
<tr>
<td>Femoral neck T score</td>
<td>−1.1 ± 1.3</td>
<td>−0.07 ± 1.6</td>
<td>0.01</td>
</tr>
<tr>
<td>BUA, dB/MHz</td>
<td>107 ± 11</td>
<td>113 ± 10</td>
<td>0.07</td>
</tr>
<tr>
<td>SOS, m/s</td>
<td>1520 ± 30</td>
<td>1548 ± 33</td>
<td>0.001</td>
</tr>
<tr>
<td>SI</td>
<td>71 ± 22</td>
<td>85 ± 22</td>
<td>0.01</td>
</tr>
</tbody>
</table>

(BUA) and speed of sound (SOS). A third variable, the stiffness index (SI), that is, a combination of both BUA and SOS, was also calculated.

Finally, biological markers of bone turnover were also measured. Serum osteocalcin (OC) and bone alkaline phosphatase (BAP) indicated bone formation, whereas type I C-terminal telopeptide (ICTP) and urinary type I collagen C-telopeptide breakdown products (second urine void, CTX) indicated bone resorption. Blood and urine samples were collected between 7:30 AM and 9:00 AM after an overnight fast. Serum samples were stored frozen at −80° until assay.

The control group consisted of 48 age and sex matched subjects recruited among health care staff members and patients who attended the clinic for disorders unrelated to bone (i.e., low back pain or sciatica without osteoarthritis on radiographs). The following variables were measured in control patients: BMD, BUA, SOS, SI, and biological markers of bone turnover.

Neither patients nor controls were receiving drugs that could affect bone mass or bone metabolism and particularly corticosteroids.

We found a borderline significant decrease for BMD in patients with PsA compared with control patients (Table 1) at both the lumbar spine (−6.0% (95% CI −12.9% to 0.9%, p = 0.08) and femoral neck: −7.4% (95% CI −15.1% to 0.3%, p = 0.06). We also found a significant decrease in patients with PsA compared with controls for both SOS: −1.8% (95% CI −15.1% to 0.7%, p = 0.01) and SI: −17.8% (95% CI −29.7% to 5.9%, p = 0.004). BUA was not significantly decreased in patients with PsA: −4.7% (95% CI −9.9% to 4.4%, p = 0.07). The sole marker of bone turnover significantly different for PsA patients compared with control patients was ICTP: 4.81 ± 1.50 versus 3.23 ± 1.39 ng/ml, respectively; p < 0.01.

Significant correlations were found for PsA patients between BMD and age at both the lumbar spine (r = −0.33, p < 0.05) and femoral neck (r = −0.5, p < 0.01). Also in the PsA group BMD was significantly correlated with body mass index (BMI) at the lumbar spine (r = 0.32, p < 0.05) and femoral neck (r = 0.45, p < 0.01). SI was significantly correlated with age (r = −0.37, p < 0.05) but with neither SOS nor BUA. Quantitative US measurements were not correlated with BMI. Neither BMD (at lumbar spine and femoral neck) nor quantitative US measurements were correlated with clinical and biologic measures of activity or severity of PsA, nor with calcium intake, alcohol consumption, or level of physical activity.

Both BAP and ICTP were correlated with CRP level: r = 0.3, p < 0.05 and r = 0.57, p < 0.01, respectively. In the same manner BAP and ICTP were correlated with ESR: r = 0.31, p < 0.05 and r = 0.75, p < 0.01.

Thus our study favored a slight (but not significant) decrease in BMD for patients with PsA in contrast with the study by Frediani, et al., but in accord with another recent study. Moreover, our quantitative ultrasound measurements are in agreement with those of Frediani, et al. and suggest that this tool is useful for assessing bone involvement in PsA. Other studies are needed for data on low bone mass in PsA.

References


To the Editor:

We read the interesting article by Frediani, et al on bone mineral density (BMD) in patients with psoriatic arthritis (PsA). We had previously reported on this topic[1]. We describe our additional experience in order to complete the information reported by Frediani, et al, as our study was also performed using dual energy x-ray absorptiometry (DEXA), which has become the preferred technique for detecting osteopenia.

We studied 52 patients with active non-exal PsA and 52 controls matched for sex, age, and menopause status; all controls were patients with soft tissue rheumatism who were otherwise healthy. Patients were divided into 3 groups: men (n = 19), premenopausal women (n = 14), and postmenopausal women (n = 19). No patient had previously received steroid treatment; all were undergoing nonsteroidal antiinflammatory drug therapy.

Table 1. Demographic, clinical, and densitometric data in patients with PsA and controls.

<table>
<thead>
<tr>
<th></th>
<th>PsA (Mean (SD))</th>
<th>Control (Mean (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>51.9 (8.5)</td>
<td>51.4 (10.5)</td>
</tr>
<tr>
<td>Duration of PsA, yrs</td>
<td>7.7 (7.6)</td>
<td>—</td>
</tr>
<tr>
<td>Lumbar spine BMD, g/cm²</td>
<td>0.908 (0.130)</td>
<td>0.918 (0.133)</td>
</tr>
<tr>
<td>Femoral neck BMD, g/cm²</td>
<td>0.738 (0.159)</td>
<td>0.781 (0.118)</td>
</tr>
<tr>
<td>Premenopausal women</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>37.6 (5.8)</td>
<td>41.7 (10.5)</td>
</tr>
<tr>
<td>Duration of PsA, yrs</td>
<td>3.3 (1.5)</td>
<td>—</td>
</tr>
<tr>
<td>Lumbar spine BMD, g/cm²</td>
<td>0.983 (0.109)</td>
<td>0.971 (0.126)</td>
</tr>
<tr>
<td>Femoral neck BMD, g/cm²</td>
<td>0.805 (0.115)</td>
<td>0.780 (0.113)</td>
</tr>
<tr>
<td>Postmenopausal women</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>58.3 (7.1)</td>
<td>58.4 (6.6)</td>
</tr>
<tr>
<td>Years since menopause</td>
<td>10.4 (7.7)</td>
<td>10.2 (5.8)</td>
</tr>
<tr>
<td>Duration of PsA, yrs</td>
<td>5.9 (5.4)</td>
<td>—</td>
</tr>
<tr>
<td>Lumbar spine BMD, g/cm²</td>
<td>0.856 (0.109)</td>
<td>0.862 (0.145)</td>
</tr>
<tr>
<td>Femoral neck BMD, g/cm²</td>
<td>0.639 (0.162)</td>
<td>0.731 (0.096)</td>
</tr>
</tbody>
</table>

* Significant difference (p < 0.05) versus the control group.
and 19 (36%) were receiving disease modifying antirheumatic drugs. BMD (g/cm²) at the lumbar spine (L₁-L₄) and femoral neck was measured by DEXA with a Hologic QDR 1000 unit. Table 1 shows the demographic, clinical, and densitometric data of patients and controls.

In the overall PaA population, disease duration (mean 5.9 (SD 5.8) years) was negatively correlated with BMD at lumbar spine (r = -0.39) and femoral neck (r = -0.29); erythrocyte sedimentation rate (mean 17.8 (SD 13.6) mm/h) was not correlated with BMD. According to the World Health Organization categories, 22 (42%) patients presented low bone mass (osteopenia) and 7 (13%) patients osteoporosis at the lumbar spine; 23 (44%) patients presented low bone mass and 4 (8%) patients osteoporosis at the femoral neck.

We agree with Frediani, et al that it would be interesting to conduct longitudinal studies to assess the problem of bone loss in patients with PaA.

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Dr. Frediani replies
To the Editor:

I have read with much interest the studies by Cortet and Nolla. Cortet's study noted a difference between the results obtained by quantitative ultrasonic (QUS) and those obtained by dual energy x-ray absorptiometry (DEXA). This difference was not noted in our study. Nor did we note this difference between DEXA and QUS in other studies we carried out in patients with rheumatoid arthritis or with postmenopausal osteoporosis. In our study of the 2 methods (QUS and DEXA) we employed equipment manufactured by Lunar, and this could be important. In Nolla's study the osteoporosis seemed to be present only at the femoral level, and only in subjects in menopause. It could be important to know the activity of the disease in premenopausal patients: in our subjects the disease was probably more severe. Indeed, in all our patients there was severe synovitis, shown by ultrasonography, in at least 5 joints.

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An Open-label, Phase I/II Study of 5-Fluorouracil Plus Leucovorin in the Treatment of Rheumatoid Arthritis

To the Editor:

Anecdotal experience in treating patients with metastatic colorectal cancer who coincidentally had rheumatoid arthritis (RA) suggests that 5-fluorouracil (5-FU) plus leucovorin (LCV) leads to improvement in patients' symptoms of RA. This observation led us to study the combination of 5-FU plus LCV in patients with active RA. We followed a treatment protocol similar to that used successfully and with acceptable toxicity in patients with metastatic colorectal cancer. The goals of this 24 week, open label pilot study were to determine the maximum tolerated dose of 5-FU, define the toxicity of this combination, and document any clinical benefit in patients with RA.

Study inclusion criteria included RA according to the 1987 classification criteria, positive rheumatoid factor, and active disease defined as ≥ 9 swollen joints plus ≥ 6 tender joints plus a Westergen sedimentation rate > 27 mm/h. A total of 9 patients (4 male, 5 female; mean age 55.1 yrs, range 48-62) were treated; 6 patients were in American College of Rheumatology (ACR) functional class 2, and 3 in functional class 3. Mean disease duration was 12.8 years (range 1.5-24). Patients had taken a mean of 3.5 disease modifying antirheumatic drugs (DMARD), 7/9 were taking prednisone at a dose of ≤ 15 mg/day, and all were receiving but failing, conventional solo DMARD therapy with methotrexate (MTX) at the screening visit for this study. MTX was discontinued 2 weeks prior to the first dose of the study drug. The prednisone dose was held constant during the study. An SGOT and complete blood count were obtained prior to each dose of the study drug.

Treatment consisted of intravenous LCV plus 5-FU given 5 consecutive days every 4 weeks for 24 weeks. Leucovorin dosage was constant at 20 mg/m² given as an intravenous bolus. The first 6 patients received 200 mg/m² of 5-FU. Because there was no appreciable toxicity at that dosage, the next 6 patients were to receive 300 mg/m² of 5-FU plus LCV. Because of the striking and consistent observations by each patient that their maximum benefit from treatment was at about 14 days after each treatment sequence, with marked worsening thereafter, we did not feel we could ethically continue the study as designed. The study was therefore terminated after 3 patients received the increased 5-FU dosage of 300 mg/m².

At baseline, the mean tender joint count was 28.2 (range 8-49), mean swollen joint count 26.1 (range 10-41), and mean Westergen sedimentation rate 44.7 mm/h (range 27-74). Swollen joint scores improved dramatically in 5/9 patients, decreasing from a mean of 32.4 to a mean of 11 (66%) by the end of the followup period at 24 weeks. However, the mean swollen joint count for all patients was 25.1 at entry, and 28 at the end of the study, while the mean tender joint count was 28.2 at entry and 23.2 by week 24. Only 3/9 patients had improvement by ACR20 criteria. Westergen sedimentation rates did not mirror clinical improvement and were unchanged at 24 weeks (mean 42.4 mm/h).

Because most patients came from some distance, only monthly clinical observation by the study physician was possible. All patients reported feeling best at about 14 days after each treatment sequence but we have no clinical observation data from those intervals. As an example of the swollen joint count in a patient with good response, the initial count was 29; 12 at week 4, 10 at week 8, 2 at week 12, 7 at week 16, 5 at week 20, and 7 at week 24.

No serious toxicity requiring discontinuation or alteration of dosage schedules was noted in any patient. One patient fell and suffered a hip fracture requiring surgery and completed only 4 of 6 treatments. Another had transient blue fingertips at 8 weeks into the study that resolved spontaneously. Six patients had minor transient nausea or diarrhea during drug infusions; one of these patients developed transient minor mouth ulcers after 2 treatment sequences, and another had minor headaches briefly during 2 treatments. No treatment related hematopoietic or hemolytic toxicities occurred.

MTX has proven to be a very useful drug in RA, yet only about 19% of patients improve by ACR50 criteria, and only 39% improve by ACR20, although in early disease improvement by ACR20 may be seen in about two-thirds of patients. 5-FU, like MTX, is an anti-metabolite and much of its effects are due to inhibition of DNA synthesis. This inhibition can be enhanced by increasing levels of reduced folate in target cells, an effect of LCV. In addition to its anti-tumor activity, 5-FU has immunosuppressive
properties. It also increases apoptosis, which may be relevant to disease activity in RA.

This open label study, with the shortcomings inherent in this design, suggested the possibility of a beneficial treatment effect of 5-FU, with an acceptable side effect profile for some patients, but the results were not compelling. Intravenous treatment for 5 consecutive days is cumbersome. While 5-FU may hold some promise for improving disease control in some patients with RA, the temporary improvement noted by many patients at 2 weeks following drug administration suggests that a more prolonging dosing approach would be beneficial. Since the completion of this pilot trial, ceftarabine, an oral formulation of 5-FU has been approved for treatment of patients with metastatic breast and colorectal cancer. This treatment, which is commonly given for 2 out of every 3 weeks, may be reasonable to evaluate in patients with RA that are resistant to conventional therapy.

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Bisphosphonate Addition to Stable Hormone Replacement Therapy Increases Bone Mineral Density in Postmenopausal Women

To the Editor:

Numerous studies have described the efficacy of hormone replacement therapy (HRT) in preventing the progression of osteoporosis, increasing bone mineral density (BMD), and decreasing incidence of fractures. On the other hand, Komulainen, et al found between 11 and 26% of women after 5 years of HRT were densitometric nonresponders at both the lumbar spine and femoral neck. We investigated if the addition of a bisphosphonate, either alendronate or etidronate, would increase BMD at the lumbar spine, greater trochanter, or femoral neck in postmenopausal women undergoing stable HRT.

Patients were chosen from the Canadian Database of Osteoporosis and Osteopenia (CANDOO). This database is accumulated from standardized forms completed prospectively for each patient with osteopenia or osteoporosis seen in consultation and follow-up at a tertiary care bone disease referral center.

All women who presented with BMD evidence of osteopenia (T score < -1 to -2.5) or osteoporosis (T score < -2.5) from 1990 until 1998 were identified. BMD was measured at the lumbar spine, femoral neck, and greater trochanter by dual x-ray absorptiometry. From this cohort of 5066 patients, we selected postmenopausal women who had been undergoing continual estrogen therapy as a single agent, or with a progestin (for those with a uterus), for at least 2 years, with documented BMD data in our database after 2 consecutive years of HRT. This timepoint was denoted the baseline. Further, to qualify for the study, this cohort of women had to have taken HRT with or without a bisphosphate (alendronate 10 mg or cyclic etidronate) for the following year from their baseline, with a followup BMD at the end of the one year.

Women were classified into 3 groups depending on the type of treatment they received the following year. The groups included: (1) continuing hormone replacement (HRT) alone (n = 249), (2) hormone replacement with the addition of alendronate (HRT + A) (n = 30), or (3) hormone replacement with the addition of intermittent cyclical etidronate (HRT + E) (n = 37). Patients were excluded if they had taken medications known to affect bone metabolism such as calcitriol, fluoride, corticosteroids, or anti convulsants during the stable estrogen or followup phase of the study.

Baseline characteristics and BMD at one year followup of the 3 groups were compared using one-way analysis of variance and Tukey’s honestly significant difference for pairwise comparisons. Baseline differences between groups were seen in age, years in menopause, calcium and vitamin D intake per day, and baseline BMD at the lumbar spine, femoral neck and greater trochanter (Table 1).

The multiple regression technique of analysis of covariance was subsequently used to analyze the BMD at one year followup, to take into account these baseline differences between groups, with the Bonferroni test to adjust for multiple comparisons. The analysis revealed that treatment with a bisphosphonate in addition to HRT led to an increase in BMD, compared with HRT alone. Differences between treatment groups in BMD at the lumbar spine: HRT + A vs HRT: +3.7% (p < 0.001), HRT + E vs HRT: +5.9% (p < 0.001), and HRT + E vs HRT + A: +4.2% (p = 1.0); at the femoral neck: HRT + A vs HRT: +2.6% (p = 0.088), HRT + E vs HRT: +4.9% (p = 1.0), and HRT + A vs HRT + E: +1.7% (p = 0.808); and at the greater trochanter: HRT + A vs HRT: +2.1% (p = 0.129), HRT + E vs HRT: +3.2% (p = 0.012), and HRT + E vs HRT + A: +1.1% (p = 1.0) (Figure 1). There were no differences in the occurrence of new fractures.

Although this was not a randomized study, our results are closely comparable to 2 randomized controlled trials showing that both etidronate and alendronate were effective in increasing BMD when added to ongoing HRT. The CANDOO database, as evident in this study, is useful for direct comparisons between multiple drugs. Ours is the first study to directly compare the effectiveness of adding etidronate or alendronate, following the use of HRT alone, on BMD. It is also the first to describe the effective-
Table 1. Baseline characteristics of the 3 treatment groups. All values represent mean (standard deviation).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HRT, n = 249</th>
<th>HRT + A, n = 30</th>
<th>HRT + E, n = 37</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>59 (9.0)</td>
<td>60 (7.0)</td>
<td>64 (8.8)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Age at menopause, yrs</td>
<td>44 (8.2)</td>
<td>45 (8.0)</td>
<td>44 (7.2)</td>
<td>0.646</td>
</tr>
<tr>
<td>Time in menopause, yrs</td>
<td>16 (9.2)</td>
<td>15 (9.3)</td>
<td>20 (8.6)</td>
<td>0.045*</td>
</tr>
<tr>
<td>Time on HRT, yrs</td>
<td>5.2 (5.8)</td>
<td>6.2 (5.4)</td>
<td>6.5 (5.6)</td>
<td>0.381</td>
</tr>
<tr>
<td>Calcium intake/day, mg</td>
<td>825 (638)</td>
<td>1132 (624)</td>
<td>1045 (606)</td>
<td>0.012*</td>
</tr>
<tr>
<td>Vitamin D intake/day, IU</td>
<td>83 (199)</td>
<td>252 (313)</td>
<td>143 (287)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26 (4.6)</td>
<td>24 (3.4)</td>
<td>26 (3.9)</td>
<td>0.179</td>
</tr>
<tr>
<td>Smoking, yrs</td>
<td>29 (13.5)</td>
<td>29 (13.8)</td>
<td>39 (11.5)</td>
<td>0.094</td>
</tr>
<tr>
<td>Caffeine per day, cups</td>
<td>2.6 (2.0)</td>
<td>2.3 (1.8)</td>
<td>2.0 (1.9)</td>
<td>0.347</td>
</tr>
<tr>
<td>Exercise, min/wk</td>
<td>35.2 (38.0)</td>
<td>32.0 (20.1)</td>
<td>27.5 (22.7)</td>
<td>0.620</td>
</tr>
<tr>
<td>Baseline BMD, g/cm²</td>
<td>0.97 (0.14)</td>
<td>0.92 (0.17)</td>
<td>0.88 (0.01)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0.76 (0.01)</td>
<td>0.70 (0.01)</td>
<td>0.71 (0.01)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>0.66 (0.10)</td>
<td>0.59 (0.01)</td>
<td>0.62 (0.11)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Greater trochanter</td>
<td>0.66 (0.10)</td>
<td>0.59 (0.01)</td>
<td>0.62 (0.11)</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

* Significant difference was seen between the HRT and HRT + E groups only.
* Significant difference was seen between the HRT and HRT + A groups only. HRT: hormone replacement therapy; BMI: body mass index; BMD: bone mineral density.

Figure 1. Percentage change from baseline to one-year followup within each treatment group at the lumbar spine, femoral neck, and greater trochanter. *Significant difference (p < 0.001) relative to HRT group. **Significant difference (p = 0.012) relative to HRT group.

ness of combination therapy, whose efficacy has been shown under clinical trial conditions, in clinical practice. Additional features of our cohort study design include the ability to analyze endpoints at lesser expense and within a shorter time than is possible in a randomized controlled trial. Such results could be used to generate hypotheses for future randomized controlled trials.

Thus, the addition of either intermittent cyclical etidronate or alendronate to stable estrogen therapy can significantly increase a postmenopausal woman's trabecular BMD. Both alendronate and etidronate were effective at the lumbar spine. Etidronate was also effective in increasing BMD at the greater trochanter. No statistically significant differences were observed between the effectiveness of the 2 bisphosphonates compared to each other.

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Infliximab for Systemic Onset Juvenile Idiopathic Arthritis: Experience in 3 Children

To the Editor:

The tumor necrosis factor-α (TNF-α) blockers infliximab and etanercept are now licensed for the treatment of refractory rheumatoid arthritis, but experience with TNF-α blockade in juvenile idiopathic arthritis (JIA) is limited. The heterogeneity of JIA disease phenotypes indicates that the pathogenesis — and the role of TNF-α — may be different. We describe 3 patients treated with infliximab for systemic onset JIA.

Patient A (girl age 18 yrs), Patient B (girl age 11 yrs), and Patient C (boy age 10 yrs) were diagnosed with systemic onset JIA at the ages of 11, 3, and 5, respectively. They received combined treatment with nonsteroidal antiinflammatory drugs (NSAID), corticosteroids, high dose methotrexate (MTX) (25 mg/m² once weekly, discontinued in Patient A because of gastrointestinal side effects), and cyclosporin A (CSA; Patients B and C). Both girls' systemic features remitted 2 years after onset, but destructive polyarthritis persisted. Patient C experienced a continuing systemic and poly-
articular course. All patients experienced growth retardation and osteoporosis. Infliximab was started at 3 mg/kg at Weeks 0, 2, and 6, followed by infusion every 8 weeks. NSAID, CsA, and MTX were continued throughout treatment. Each clinical visit included assessment of active joint number (AJN, joints with swelling not due to deformity or with limited motion and with pain, tenderness, or both), joints with limited motion (LJN), visual analog scale measurement (parent assessment) for global well being (VASp) and pain (VASp) (scale 0–100 mm), Childhood Health Assessment Questionnaire (CHAQ), and serum C-reactive protein (CRP) and interleukin 6 (IL-6) (Patient C).

Infliximab induced rapid and sustained control of polyarthritis in Patients A and B, as evidenced by decreasing clinical, biochemical, and functional scores (Figure 1). In Patient A, steroid dose (0.2 mg/kg/day) was reduced by 50%; it was unchanged in Patient B (0.2 mg/kg/day). Strikingly, in Patient B, infliximab treatment resulted in an apparent repair process of the damaged hip joints. Six months before infliximab treatment, the hip radiograph showed severe joint space narrowing and erosions; reevaluation at Week 37 showed improvement in joint space, indicating gain of articular cartilage (Figure 2). During infliximab therapy, the girl, who was wheelchair-bound, regained the ability to walk independently.

In Patient A, LJN changed minimally, suggesting irreversible joint damage; the decrease in CRP lagged behind the clinical improvement. A self-limited rhinitis in Patient B (Figure 1) was associated with an increased CHAQ score but not with arthritis relapse, suggesting that infection related malaise, rather than arthritis, was the major determinant of the CHAQ score. This is in accord with the report by Ruperto, et al, who found the LJN, CHAQ, and biochemical measures to be less sensitive for assessment of disease activity in JIA. A slightly modified definition of improvement, proposed by Giannini, et al, was used: we considered patients as responders when 30% or greater improvement was noted in at least 3 of 5 variables, with no more than one variable worsening by 30% or more. Accordingly, Patients A and B were considered to be responders.

A similar favorable response of polyarthritis was observed in Patient C. However, systemic features failed to respond to 3 and 5 mg/kg infliximab (Figure 1). Elliott, et al reported temporary control of systemic disease but not of polyarthritis by 2 doses of 10 mg/kg infliximab in a similar patient. An abstract on the use of etanercept in systemic JIA notes remission of systemic features in 23 out of 36 patients (survey by questionnaire); a variable response to etanercept was reported in another abstract. In our patient, systemic disease seemed to remit following a dose increase to 10 mg/kg, but at Week 67 high fever recurred, paralleled by high CRP and IL-6 levels, and arthritis reappeared. The CsA dose (0.5 mg/kg/day), which had been reduced by 40%, was increased again. Systemic disease and arthritis functional scores improved only with intensive physiotherapy — mechanical joint damage may have affected subjective and functional scoring. Overall, Patient C was found to be a nonresponder.

Possible adverse reactions of infliximab therapy were self-limited upper airway infections (Patient B one, Patient C 3).

![Figure 1](https://www.jrheum.org)
Numerous investigators have reported on the expression of pro- and anti-inflammatory cytokines in synovial fluid and serum of patients with JIA, and have tried to characterize cytokine profiles in different JIA subtypes that may be related to their pathogenesis\textsuperscript{a}. Increasing evidence suggests IL-6 is largely responsible for the extraarticular features of systemic JIA\textsuperscript{a}. The fluctuating levels of both CRP and IL-6 in Patient C support this hypothesis and reflect failure of chronic pulsed TNF-\(\text{\ensuremath{\alpha}}\) antagonism to control the acute phase response typical of systemic JIA.

Our experience suggests infliximab may be effective for polyarthritis in systemic onset JIA when systemic symptoms are controlled or absent, whereas it may not control systemic disease activity at doses up to 10 mg/kg. Discordance of the arthritic compared to the systemic disease response suggests that different cytokine networks may operate in these disease components and supports the view that several cytokines, such as TNF-\(\text{\ensuremath{\alpha}}\) and IL-6, may be potential targets for immunotherapy in JIA.

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Book review

Osteoarthritis: Diagnosis and Medical/Surgical Management, 3rd edition.


Osteoarthritis in its 3rd edition continues the excellent tradition established since it was first published in 1984. It has been revised with deletions and additions to reflect current knowledge and advances. In particular, the basic science section is a wonderful addition and reviews all the current issues relating to etiopathogenesis. Consideration of the genetics of osteoarthritis and the joint as an organ is most useful. The advances in imaging techniques are well reflected in the chapters concerning diagnosis. Noninvasive markers of diagnosis and disease evolution are reviewed. The concept of disease modification is approached in detail, and with this new approach osteoarthritis indeed has come into its own in the new millennium. Neuroucrea are a given realistic review. A well thought out presentation of surgical approaches takes into account both technical detail and goals and objectives of surgery and potential results. There is an excellent discussion in at least 2 areas of clinical trials relevant to osteoarthritis.

This volume is an excellent reference book. It is written in a coherent and straightforward manner and should be considered the major text for discussion of all aspects of osteoarthritis. Its contributors and authors are leaders in their fields of discipline and bring to the volume the most up-to-date information. The book is highly recommended to rheumatologists and to all those who are involved in the management of osteoarthritis.

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